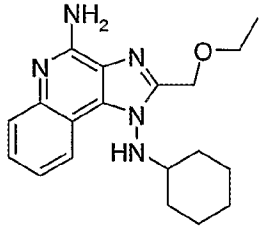
J = 8.2, 1.1 Hz, 1 H), 7.77 (dd, J = 8.4, 0.7 Hz, 1 H), 7.54-7.47 (m, 1 H), 7.33-7.24 (m, 1 H), 5.55 (d, J = 3.2 Hz, 1 H), 5.41 (s, 2 H), 4.89 (s, 2 H), 3.73-3.60 (m, 3 H), 1.26 (t, J = 7.0 Hz, 3H); 1.15 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 148.7, 145.0, 127.7, 126.6, 123.9, 121.9, 121.3, 115.4, 66.8, 65.7, 52.5, 20.6, 15.1; MS m/z 300 (M + H)$^+$; Anal. Calcd for $C_{16}H_{21}N_5O \cdot 0.48\ H_2O$: C, 62.39; H, 7.19; N, 22.74; Found: C, 62.38; H, 6.90; N, 22.79.

Example 6

N^1-Cyclohexyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

2-(Ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.900 g, 3.71 mmol) was placed in a 50 mL round bottom flask, dissolved in 1,2-dichloromethane, and placed under N_2. Cyclohexanone (1.19 mL, 11.5 mmol), acetic acid (0.45 mL, 7.79 mmol) and sodium triacetoxyborohydride (1.65 g, 7.79 mmol) were added and the reaction was stirred under N_2 at room temperature for 5 days. The reaction was quenched by slow addition of saturated $NaHCO_3$ solution (25 mL) and dichloromethane (25 mL). The mixture was transferred to a separatory funnel and the phases separated. The aqueous portion was extracted with dichloromethane (25 mL). The combined organic portions were washed sequentially with water (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and then concentrated to yield a thick brown oil. Analysis by liquid chromatography/mass spectroscopy (LC/MS) of the crude product showed it to be a mixture of the hydrazone and hydrazine. The oil was dissolved in methanol (25 mL), chilled in an ice water bath and then treated with sodium borohydride (1.25 g). The reaction was quenched with water (25 mL) and the mixture concentrated. The residue was partitioned between dichloromethane 50 mL) and water (15 mL), transferred to a separatory funnel, and the phases were separated. The organic portion was washed sequentially with saturated $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and

then concentrated to yield a thick brown oil. The material was purified by column chromatography (35 g SiO_2, 97:3 chloroform:methanol) to yield 0.51 g of *N*-cyclohexyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a light brown oil / solid.

Part B

N-Cyclohexyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.51 g, 1.57 mmol) was placed in a 200 mL round bottom flask, purged with N_2 and dissolved in dichloromethane (25 mL). MCPBA (0.484 g, 1.96 mmol, 77% max) was added over a 5 min period. The reaction was stirred at room temperature under N_2. After 2 h, analysis by thin layer chromatography (TLC) (SiO_2, 95:5 chloroform:methanol) showed complete conversion. The solution was diluted with dichloromethane (15 mL) and 2% sodium carbonate solution (15 mL). The mixture was transferred to a separatory funnel, and the phases were separated. The organic portion was washed sequentially with 2% sodium carbonate solution (15 mL), water (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered and then concentrated to yield 0.431 g of *N*-cyclohexyl-2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a tan foam.

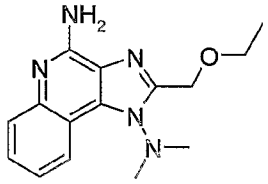
Part C

N-Cyclohexyl-2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.425 g, 1.25 mmol) was placed in a 100 mL round bottom flask and dissolved in dichloromethane (20 mL). Ammonium hydroxide solution (10 mL) was added and the mixture was stirred vigorously. The stirred mixture was chilled in an ice water bath. *Para*-toluenesulfonyl chloride (0.250 g, 1.31 mmol) was added over 5 min. After 30 min of stirring at 0 °C TLC (SiO_2, 95:5 chloroform:methanol) showed complete conversion. The mixture was warmed to room temperature and then diluted with dichloromethane (25 mL) and water (10 mL). The mixture was transferred to a separatory funnel and the phases separated. The organic portion was washed sequentially with 2% sodium carbonate solution (15 mL), water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and then concentrated to yield an orange/tan foamy solid. The material was purified by column chromatography (40 g SiO_2, 95:5 chloroform:methanol) to yield the product as an off white solid. The off-white solid was dissolved in 3 mL of a 9:1 chloroform:methanol mixture. A small spatula tip full of activated carbon (DARCO G 60-100 mesh) was added

and the mixture was stirred at room temperature for 3 h. The mixture was filtered through a short column of SiO_2 (5 g) eluting with 9:1 chloroform:methanol. The filtrate was concentrated to yield a glassy solid. The glassy solid was triturated in 15 mL diethyl ether for 2 h to provide a white solid. The solid was collected by vacuum filtration and rinsed with diethyl ether. The solid was dried in a vacuum oven (70 °C) to yield 0.062 g of N^1-cyclohexyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine. mp 143–145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (dd, J = 8.1, 1.1 Hz, 1 H), 7.58 (dd, J = 8.3, 0.9 Hz, 1 H), 7.46-7.38 (m, 1 H), 7.28-7.21 (m, 1 H), 6.99 (d, J = 1.9 Hz, 1 H), 6.69 (s, 2 H), 4.77 (s, 2 H), 3.63 (q, J = 7.0 Hz, 2 H), 3.32-3.23 (m, 1 H), 1.71-1.52 (m, 5 H), 1.30-1.05 (m, 8 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ; MS *m/z* 152.1, 150.3, 145.0, 133.4, 127.4, 125.8, 123.9, 121.6, 121.1, 115.0, 65.8, 63.1, 59.8, 30.9, 25.8, 24.3, 15.4; MS *m/z* 340 (M + H)$^+$; Anal. Calcd for $C_{19}H_{25}N_5O$: C, 67.23; H, 7.42; N, 20.63; Found: C, 67.32; H, 7.37; N, 20.55.

Example 7

N^1,N^1-Dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 4-chloro-3-nitroquinoline (5.00 g, 24.0 mmol) in 100 mL CH_2Cl_2 was cooled to 0 °C and treated with triethylamine (8.40 mL, 60.0 mmol) and *N,N*-dimethylhydrazine (5.65 mL, 74.4 mmol) under an atmosphere of nitrogen. After 18 h, the mixture was diluted with 2% Na_2CO_3 solution and $CHCl_3$ and separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 4-(2,2-dimethylhydrazino)-3-nitroquinoline (5.33 g) as a yellow/orange crystalline solid.

Part B

A suspension of 4-(2,2-dimethylhydrazino)-3-nitroquinoline (5.33 g, 23.0 mmol) in 125 mL of acetonitrile was treated with 5% platinum on carbon (0.45 g, 0.11 mmol) and the mixture was shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 5 h, the reaction mixture was filtered through a pad of CELITE filter agent and rinsed with 80:20 acetonitrile:MeOH. The filtrate was concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4-(2,2-dimethylhydrazino)quinolin-3-amine (4.64 g) as a red foam.

Part C

A solution of 4-(2,2-dimethylhydrazino)quinolin-3-amine (4.64 g, 23.0 mmol) in 75 mL of CH_2Cl_2 was cooled to 0 °C under an atmosphere of nitrogen. The reaction mixture was treated with triethylamine (6.72 mL, 48.2 mmol) followed by dropwise addition of ethoxyacetyl chloride (2.95 g, 24.1 mmol). After 1.5 h, the reaction mixture was concentrated under reduced pressure. The resulting oil was dissolved in 75 mL of ethanol, treated with triethylamine (9.60 mL, 68.9 mmol) and heated to reflux. After 5 d, the reaction mixture was concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2, washed with 2% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown oil. Chromatography (SiO_2, 5-10% MeOH/$CHCl_3$) gave *N,N*-dimethyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.89 g) as a brown oil.

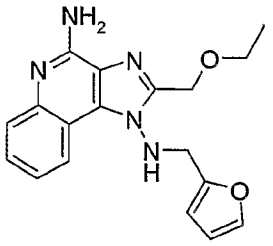
Part D

A solution of *N,N*-dimethyl-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.89 g, 3.3 mmol) in 25 mL of CH_2Cl_2 was treated with MCPBA (1.01 g, 4.10 mmol, 77% max). After 1.5 h, the reaction mixture was treated with 7 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.69 g, 3.6 mmol). After 30 min, the reaction was diluted with CH_2Cl_2 and water and the phases were separated. The organic portion was washed with 2% Na_2CO_3 solution (2X), water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield an orange solid. Recrystallization twice from acetonitrile gave N^1,N^1-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.208 g) as gold, needle-like crystals. mp 213–215

°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, J = 8.3, 1.4 Hz, 1 H), 7.79 (dd, J = 8.4, 0.7 Hz, 1 H), 7.56-7.48 (m, 1 H), 7.38-7.29 (m, 1 H), 5.45 (s, 2 H), 4.48 (s, 2 H), 3.69 (q, J = 7.0 Hz, 2 H), 3.20 (s, 6 H), 1.29 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 149.3, 145.1, 133.5, 127.7, 126.7, 123.8, 122.1, 115.3, 66.4, 65.6, 45.3, 15.1; MS (APCI) *m/z* 286 $(M + H)^+$; Anal. Calcd for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.54; Found: C, 63.02; H, 6.91; N, 24.57.

Example 8

2-Ethoxymethyl-N^1-(furan-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.50 g, 6.19 mmol) in 20 mL of isopropanol was treated with 2-furaldehyde (1.08 mL, 13.0 mmol) and 2 drops of concentrated HCl and heated to reflux under an atmosphere of nitrogen. After 48 h, the reaction was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in 30 mL of $CHCl_3$ and washed with 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(furan-2-ylmethylene)amine (1.86 g) as a light brown solid.

Part B

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(furan-2-ylmethylene)amine (1.86 g, 5.81 mmol) in 20 mL of methanol was treated with $NaBH_4$ (0.659 g, 17.4 mmol) and stirred under an atmosphere of nitrogen. After 18 h the reaction was quenched by addition of 20 mL of water. The reaction mixture was concentrated under reduced pressure and dissolved in $CHCl_3$. The organic portion was washed with 2% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under

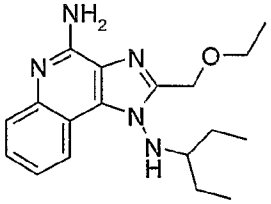
reduced pressure to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(furan-2-ylmethyl)amine (1.70 g) as a thick orange syrup.

Part C

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(furan-2-ylmethyl)amine (1.70 g, 5.27 mmol) in 45 mL of CH_2Cl_2 was treated with MCPBA (1.48 g, 6.59 mmol, 77% max). After 1.5 h the reaction mixture was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (1.06 g, 5.54 mmol). After 45 min the reaction mixture was diluted with water and $CHCl_3$ and separated. The organic portion was washed with 3% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield a yellow foam. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave an off white foam. The foam was triturated with diethyl ether and filtered to give 2-ethoxymethyl-N^1-(furan-2-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (1.03 g) as an off white powder. mp dec. > 200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.80 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.57-7.51 (m, 1 H), 7.45 (d, *J* = 1.8 Hz, 1 H), 7.39-7.33 (m, 1 H), 6.34-6.32 (m, 1 H), 6.24 (t, *J* = 5.3 Hz, 1 H), 6.07 (d, *J* = 3.1 Hz, 1 H), 5.43 (s, 2 H), 4.40-4.38 (m, 4 H), 3.57 (q, *J* = 7.0 Hz, 2 H), 1.25 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 149.5, 147.8, 144.8, 143.0, 132.6, 127.8, 126.6, 124.1, 122.5, 120.7, 115.1, 111.1, 110.1, 66.8, 64.9, 48.5, 15.0; MS (APCI) *m/z* 338 $(M + H)^+$; Anal. Calcd for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76; Found: C, 63.89; H, 5.75; N, 20.48.

Example 9

2-Ethoxymethyl-N^1-(1-ethylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.50 g, 6.19 mmol) in 20 mL of toluene and 5 mL of isopropanol was treated with 3-pentanone (5.00 mL, 47.2 mmol) and pyridinium *p*-toluenesulfonate (0.015 g, 0.062 mmol) and the reaction mixture was heated to reflux under an atmosphere of nitrogen. After 7 d, the reaction mixture was concentrated under reduced pressure, dissolved in $CHCl_3$, washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown oil. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(1-ethylpropylidene)amine (1.78 g) as a yellow/green syrup.

Part B

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(1-ethylpropylidene)amine (1.78 g, 5.73 mmol) in 20 mL of methanol was treated with $NaBH_4$ (0.867 g, 22.9 mmol) and $CeCl_3 \cdot 7H_2O$ (15 mg, catalytic) and stirred under an atmosphere of nitrogen. After 24 h, the reaction was concentrated under reduced pressure, dissolved $CHCl_3$, washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a yellow/green syrup. Chromatography (SiO_2, 93:7 $CHCl_3$:MeOH) gave *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(1-ethylpropyl)amine (1.01 g) as a yellow/green oil.

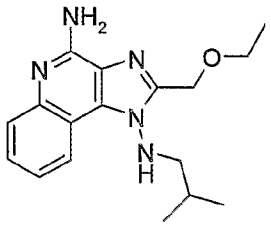
Part C

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(1-ethylpropyl)amine (1.01 g, 3.23 mmol) in 30 mL of CH_2Cl_2 was treated with MCPBA (1.04 g, 4.20 mmol, 77% max). After 1.5 h the reaction mixture was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.65 g, 3.39 mmol). After 30 min, the reaction mixture was diluted with CH_2Cl_2 and water and the phases were separated. The organic portion was washed with 2 % Na_2CO_3 solution and water. The combined aqueous washes were back extracted with $CHCl_3$ (2X). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light yellow foam. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) gave a white foam. The foam was triturated with CH_2Cl_2/hexanes and

filtered to give 2-ethoxymethyl-N^1-(1-ethylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.652 g) as a white solid. mp 125–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (dd, J = 8.3, 1.1 Hz, 1 H), 7.77 (dd, J = 7.6, 0.8 Hz, 1 H), 7.55-7.48 (m, 1 H), 7.33-7.26 (m, 1 H), 5.66, (d, J = 3.0 Hz, 1 H), 5.41 (s, 2 H), 4.87 (s, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 3.32-3.23 (m, 1 H), 1.70-1.56 (m, 2 H), 1.55-1.41 (m, 2 H), 1.27 (t, J = 7.1 Hz, 3 H), 0.94 (t, J = 7.5 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 149.1, 145.4, 135.0, 132.4, 128.1, 126.9, 124.1, 122.2, 122.0, 115.9, 67.2, 66.2, 64.0, 24.5, 15.5, 10.2; MS (APCI) *m/z* 328 $(M + H)^+$; Anal. Calcd for $C_{18}H_{25}N_5O$: C, 66.03; H, 7.70; N, 21.39; Found: C, 65.64; H, 7.89; N, 21.02.

Example 10

2-Ethoxymethyl-N^1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (0.940 g, 3.88 mmol) in 20 mL of toluene and 5 mL of isopropanol was treated with isobutyraldehyde (0.800 mL, 8.81 mmol) and pyridinium *p*-toluenesulfonate (0.098 g, 0.39 mmol) and the reaction mixture was heated to reflux under an atmosphere of nitrogen. After 48 h, the reaction mixture was concentrated under reduced pressure and dissolved in $CHCl_3$. The organic portion was washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown oil which solidified under vacuum to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isobutylideneamine (1.15 g) as a tan solid.

Part B

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isobutylideneamine (1.15 g, 3.88 mmol) in 15 mL of methanol was treated with $NaBH_4$

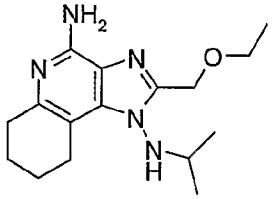
(0.44 g, 11.6 mmol) and stirred under an atmosphere of nitrogen. After 18 h, the reaction was concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ and water, and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield an orange oil. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH), gave *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isobutylamine (0.69 g) as clear, colorless crystals.

Part C

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isobutylamine (1.16 g, 3.89 mmol) in 30 mL of CH_2Cl_2 was treated with MCPBA (1.25 g, 5.05 mmol, 77% max). After 1.5 h, the reaction mixture was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.78 g, 4.08 mmol). After 30 min the reaction mixture was diluted with CH_2Cl_2 and water, and the phases were separated. The organic portion was washed with 2% Na_2CO_3 solution and water. The combined aqueous washes were back extracted with $CHCl_3$ (2X). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown foam. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) yielded 2-ethoxymethyl-N^1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.049 g) as an off white solid. mp 137–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 350 K) δ 8.47 (dd, J = 8.1, 0.9 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H), 7.45-7.36 (m, 1 H), 7.28-7.19 (m, 1 H), 6.67, (t, J = 6.2 Hz, 1 H), 6.22 (s, 2 H), 4.76 (s, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 3.02 (t, J = 6.4 Hz, 2 H), 1.97 (s, J = 6.7 Hz, 1 H), 1.19 (t, J = 7.0 Hz, 3 H), 1.05 (d J = 6.7 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.9, 148.9, 144.8, 131.9, 126.9, 125.7, 123.8, 120.8, 114.2, 65.4, 62.8, 59.6, 26.7, 20.5, 14.9; MS (APCI) *m/z* 314 $(M + H)^+$; Anal. Calcd for $C_{17}H_{23}N_5O$: C, 65.15; H, 7.40; N, 22.35; Found: C, 64.88; H, 7.39; N, 22.38.

Example 11

2-Ethoxymethyl-N^1-isopropyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine

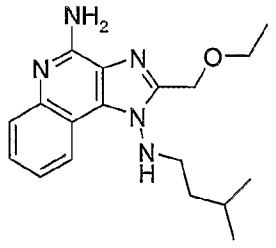


Part A

A solution of 2-ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.700 g, 2.34 mmol) in 25 mL of trifluroacetic acid was treated with platinum(IV) oxide (0.27 g, 1.2 mmol) and the mixture was shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 15 h, the reaction mixture was filtered through a pad of CELITE filter agent, rinsed with 9:1:0.5 $CHCl_3$:MeOH:trifluoroacetic acid (TFA) and concentrated under reduced pressure to yield a creamy white solid. The solid was triturated with concentrated NH_4OH solution for 2 h and then extracted with $CHCl_3$ (3X). The organic portion was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a white foam. The foam was triturated with diethyl ether, filtered and dried under reduced pressure to yield 2-ethoxymethyl-N^1-isopropyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.376 g) as a fine white solid. mp 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (d, J = 2.7 Hz, 1 H), 4.92 (s, 2 H), 4.78 (s, 2 H), 3.61 (q, J = 7.0 Hz, 2 H), 3.53-3.43 (m, 1 H), 3.07-3.03 (m, 2 H), 2.85-2.81 (m, 2 H), 1.92-1.79 (m, 4 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.08 (d, J = 6.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 148.9, 148.1, 138.8, 122.9, 107.4, 66.6, 65.4, 53.0, 32.5, 23.7, 23.2, 22.8, 20.5, 15.1; MS (APCI) *m/z* 304 $(M + H)^+$; Anal. Calcd for $C_{16}H_{25}N_5O$: C, 63.34; H, 8.31; N, 23.08; Found: C, 63.32; H, 8.31; N, 22.97.

Example 12

2-Ethoxymethyl-N^1-(3-methylbutyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.00 g, 4.13 mmol) in 20 mL of toluene and 5 mL of isopropanol was treated with isovaleraldehyde (0.94 mL, 8.76 mmol) and pyridinium *p*-toluenesulfonate (0.052 g, 0.21 mmol) and the

reaction mixture was heated to reflux under an atmosphere of nitrogen. After 15 h, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in $CHCl_3$ and washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(3-methylbutylidene)amine (1.28 g) as a dark orange oil.

Part B

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(3-methylbutylidene)amine (1.28 g, 4.13 mmol) in 25 mL of methanol was treated with $NaBH_4$ (0.47 g, 12.39 mmol). After 1 h, the reaction was quenched with saturated NH_4Cl solution and the mixture was concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ and saturated $NaHCO_3$ solution and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(3-methylbutyl)amine (1.24 g) as a dark orange oil.

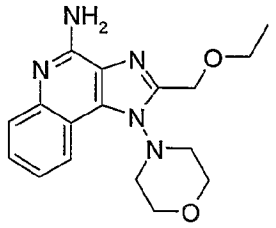
Part C

A solution of *N*-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)(3-methylbutyl)amine (1.24 g, 3.97 mmol) in 45 mL of CH_2Cl_2 was treated with MCPBA (1.87 g, 7.04 mmol, 77% max). After 1.5 h, the reaction mixture was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.795 g, 4.17 mmol). After 30 min, the reaction mixture was diluted with $CHCl_3$ and water and the phases were separated. The organic portion was washed with 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a sticky orange foam. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) gave an off white foam. The foam was triturated with diethyl ether and hexanes and filtered to give 2-ethoxymethyl-N^1-(3-methylbutyl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.435 g) as a cream colored solid. mp 129–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, J = 8.1, 1.1 Hz, 1 H), 7.78 (d, J = 8.3 Hz, 1 H), 7.56-7.50 (m, 1 H), 7.36-7.30 (m, 1 H), 5.59 (t, J = 6.7 Hz, 1 H), 5.42 (s, 2 H), 4.87 (s, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 3.29 (q, J = 7.0 Hz, 2 H), 1.76 (s, J = 6.7 Hz, 1 H), 1.60 (q, J = 6.9 Hz, 2 H), 1.27 (t, J = 7.0 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 147.8, 144.9, 133.1, 127.8, 126.6, 124.0, 122.3, 120.7,

115.2, 66.8, 65.3, 51.1, 36.7, 26.0, 22.6, 15.1; MS (APCI) *m/z* 328 $(M + H)^+$; Anal. Calcd for $C_{18}H_{25}N_5O \cdot 0.06H_2O$: C, 65.81; H, 7.71; N, 21.32; Found: C, 65.42; H, 7.75; N, 21.11. Karl Fischer analysis 0.32% water.

Example 13

2-Ethoxymethyl-1-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A solution of 4-chloro-3-nitroquinoline (5.00 g, 24.0 mmol) in 100 mL of CH_2Cl_2 was treated with triethylamine (6.37 mL, 48.0 mmol) and 4-aminomorpholine (3.47 mL, 36.0 mL) under an atmosphere of nitrogen. After 15 h, the reaction mixture was diluted with 5% Na_2CO_3 solution and $CHCl_3$, and the phases were separated. The organic portion was washed with another portion of 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a bright yellow solid. Recrystallization from acetonitrile gave *N*-(morpholin-4-yl)(3-nitroquinolin-4-yl)amine (4.54 g) as bright yellow needle-like crystals.

Part B

A solution of *N*-(morpholin-4-yl)(3-nitroquinolin-4-yl)amine (4.54 g, 16.6 mmol) in 150 mL of toluene was treated with 5% platinum on carbon (0.65 g, 0.17 mmol) and the mixture was shaken under an atmosphere of hydrogen (3.8×10^5 Pa). After 15 h, the reaction mixture was filtered through a pad of CELITE filter agent and rinsed with 4:1 toluene:MeOH. The filtrate was concentrated under reduced pressure to yield N^4-(morpholin-4-yl)quinoline-3,4-diamine (4.06 g) as a red foam.

Part C

A solution of N^4-(morpholin-4-yl)quinoline-3,4-diamine (4.06 g, 16.6 mmol) in 50 mL of CH_2Cl_2 was treated with triethylamine (4.40 mL, 33.2 mmol) and cooled to 0 °C. The solution was treated dropwise with ethoxyacetyl chloride (2.40 g, 17.4 mmol) and stirred under an atmosphere of nitrogen. The reaction mixture was allowed to slowly come to room temperature. After 2 d, the reaction mixture was concentrated under reduced pressure to yield a red semi-solid. The material was dissolved in $CHCl_3$ and washed with water, 5% Na_2CO_3 solution and brine, dried over Na_2SO_4, filtered and dried to yield 2-ethoxy-*N*-{4-[(morpholin-4-yl)amino]quinolin-3-yl}acetamide (5.35 g) as a red/orange foam.

Part D

A suspension of 2-ethoxy-*N*-{4-[(morpholin-4-yl)amino]quinolin-3-yl}acetamide (5.35 g, 16.2 mmol) in 65 mL of toluene was treated with pyridine hydrochloride (0.94 g g, 0.081 mmol). The reaction flask was equipped with a Dean-Stark trap and the reaction mixture was heated to reflux under an atmosphere of nitrogen. After 2.5 d, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in $CHCl_3$ and was washed with 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown foam. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave 2-ethoxymethyl-1-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinoline (1.61 g) as a light brown solid.

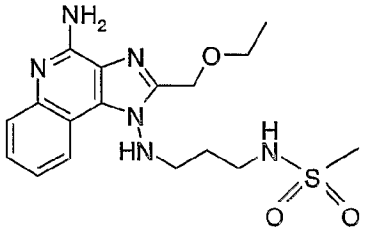
Part E

A solution of 2-ethoxymethyl-1-(morpholin-4-yl)-1*H*-imidazo[4,5-*c*]quinoline (1.61 g, 5.51 mmol) in 40 mL of CH_2Cl_2 was treated with MCPBA (1.78 g, 6.70 mmol, 77% max). After 30 min, the reaction mixture was treated with 20 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (1.03 g, 5.41 mmol). After 15 min, the reaction mixture was diluted with CH_2Cl_2 and water and the phases were separated. The organic portion was washed with 5% Na_2CO_3 solution, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a tan foam. Chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) gave a light yellow foam. The foam was triturated with diethyl ether and filtered to give 2-ethoxymethyl-1-(morpholin-4-yl)-1*H*-

imidazo[4,5-*c*]quinolin-4-amine (0.794 g) as a light cream colored solid. mp 223–224 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, J = 8.1 Hz, 1 H), 7.79 (d, J = 8.4 Hz, 1 H), 7.54 (t, J = 8.2 Hz, 1 H), 7.34 (t, J = 8.1 Hz, 1 H), 5.48 (s, 2 H), 4.85 (s, 2 H), 4.06-4.03 (m, 4 H), 3.74-3.66 (m, 4 H), 3.42-3.38 (m, 2 H), 1.29 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 149.0, 145.3, 133.5, 127.9, 126.9, 123.7, 122.2, 121.3, 115.3, 67.5, 66.5, 65.9, 53.5, 15.1; MS (APCI) *m/z* 328 $(M + H)^+$; Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.37; H, 6.47; N, 21.39; Found: C, 62.14; H, 6.19; N, 21.34.

Example 14

N-{3-[(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl} methanesulfonamide



Part A

A solution of 1-amino-3,3-diethoxypropane (5.00 mL, 30.9 mmol) in 5 mL of tetrahydrofuran (THF) was treated with triethylamine (4.51 mL, 34.0 mmol) under an atmosphere of nitrogen and cooled to 0 °C. The reaction mixture was then treated dropwise with a solution of di-*tert*-butyl dicarbonate (7.42 g, 34.0 mmol) in 25 mL of THF. The reaction mixture was stirred for 2 h at 0 °C and then allowed to come to room temperature. After 15 h, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *tert*-butyl (3,3-diethoxypropyl)carbamate (8.40 g) as a clear, faintly yellow oil.

Part B

A solution of 2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (1.00 g, 4.13 mmol) in 20 mL of acetonitrile and 5 mL of glacial acetic acid was treated with *tert*-butyl (3,3-diethoxypropyl)carbamate (2.55 g, 10.3 mmol) and heated to reflux under an

atmosphere of nitrogen. After 15 h, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was partitioned between $CHCl_3$ and saturated $NaHCO_3$ solution and the phases were separated. The organic portion was washed with water (2X) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *tert*-butyl {3-[(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)imino]propyl}carbamate (1.64 g) as a dark red/orange oil.

Part C

A solution of *tert*-butyl {3-[(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)imino]propyl}carbamate (1.64 g, 4.13 mmol) in 20 mL of methanol was treated with $NaBH_4$ (0.78 g, 20.6 mmol) under an atmosphere of nitrogen. After 1.5 h, the reaction mixture was quenched with saturated NH_4Cl solution and concentrated under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ solution and $CHCl_3$ and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown solid. Chromatography [SiO_2, 95:5 $CHCl_3$:(80:18:2 $CHCl_3$:MeOH:NH_4OH)] yielded *tert*-butyl {3-[(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}carbamate (1.34 g) as a tan foam.

Part D

A solution of *tert*-butyl {3-[(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}carbamate (1.34 g, 3.35 mmol) in 30 mL of $CHCl_3$ was treated with MCPBA (1.45 g, 5.03 mmol, 77% max). After 3 h, the reaction mixture was diluted with 10% Na_2CO_3 solution and $CHCl_3$ and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *tert*-butyl {3-[(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}carbamate (1.39 g) as an orange foam.

Part E

A solution of *tert*-butyl {3-[(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}carbamate (1.39 g, 3.35 mmol) in 35 mL of $CHCl_3$ was treated with 15 mL of concentrated NH_4OH solution and *p*-toluenesulfonyl chloride (0.67 g, 3.51 mmol).

After 15 min, the reaction mixture was diluted with water and $CHCl_3$ and the phases were separated. The organic portion was washed with 10% Na_2CO_3 solution and water. The combined aqueous washes were back-extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield {3-[(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl} *tert*-butyl carbamate (1.30 g) as an orange foam.

Part F

A solution of {3-[(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl} *tert*-butyl carbamate (1.30 g, 3.14 mmol) in 10 mL of ethanol was treated with a solution of 3 M hydrogen chloride in ethanol (5.0 mL, 15 mmol) and heated to 100 °C. After 30 min, the solvent was concentrated under reduced pressure to yield a brown sludge. The material was triturated with diethyl ether and filtered to give a tan solid. The solid was dissolved in water and treated with 10% NaOH solution until pH 13 was reached. The aqueous solution was extracted with CH_2Cl_2 (4X). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield N^1-(3-aminopropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.77 g) as a gold colored foam.

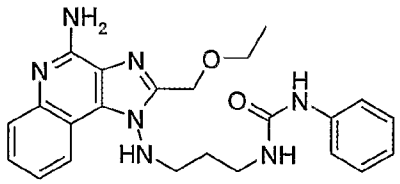
Part G

A solution of N^1-(3-aminopropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.250 g, 0.795 mmol) in 10 mL of CH_2Cl_2 was treated with triethylamine (0.221 mL, 1.67 mmol) under an atmosphere of nitrogen and cooled to 0 °C. The reaction mixture was treated dropwise with methanesulfonyl chloride (0.065 mL, 0.835 mmol). After 16 h, the reaction mixture was quenched by 10% Na_2CO_3 solution, diluted with $CHCl_3$ and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light yellow solid. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave an off-white foam. The foam was triturated with diethyl ether and filtered to give *N*-{3-[(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}methanesulfonamide (0.164 g) as an off white solid. mp 148–150 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (d, J = 7.8 Hz, 1 H), 7.58 (d, J = 8.2 Hz, 1 H), 7.44 (t, J = 7.1 Hz, 1 H), 7.25 (t, J = 7.4 Hz, 1 H),

7.05-6.95 (m, 2 H), 6.61 (s, 2 H), 4.76 (s, 2 H), 3.62 (q, J = 7.0 Hz, 2 H), 3.22 (q, J = 6.8 Hz, 2 H), 3.07 (q, J = 6.2 Hz, 2 H), 2.88 (s, 3 H), 1.78 (p, J = 6.3 Hz, 2 H), 1.18 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.3, 149.5, 145.3, 132.5, 127.4, 126.1, 124.2, 121.3, 121.3, 114.7, 65.9, 63.1, 49.9, 39.6, 28.1, 15.4; MS (APCI) m/z 393 (M + H)$^+$; Anal. Calcd for $C_{17}H_{24}N_6O_3$: C, 52.03; H, 6.16; N, 21.41; Found: C, 51.84; H, 6.28; N, 21.18.

Example 15

1-{3-[(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}-3-phenylurea



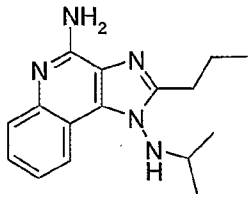
Part A

A solution of N^1-(3-aminopropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.250 g, 0.795 mmol) in 10 mL of CH_2Cl_2 was cooled to 0 °C under an atmosphere of nitrogen. The reaction mixture was treated dropwise with phenyl isocyanate (0.091 mL, 0.835 mmol). After 16 h, the reaction mixture was quenched by 10% Na_2CO_3 solution, diluted with $CHCl_3$ and the phases were separated. The organic portion was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield an off-white solid. Chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) gave an off-white foam. The foam was triturated with diethyl ether and filtered to give 1-{3-[(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amino]propyl}-3-phenylurea (0.115 g) as an off-white solid. mp 177–179 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (dd, J = 8.1, 1.0 Hz, 1 H), 8.39 (s, 1 H), 7.58 (dd, J = 8.4, 0.9 Hz, 1 H), 7.44-7.35 (m, 3 H), 7.25-7.18 (m, 3 H), 6.99 (t, J = 5.6 Hz, 1 H), 6.90-6.85 (m, 1 H), 6.60 (s, 2 H), 6.16 (t, J = 5.6 Hz, 1 H), 4.76 (s, 2 H), 3.60 (q, J = 7.0 Hz, 2 H), 3.26-3.18 (m, 4 H), 1.76 (t, J = 7.0 Hz, 2 H), 1.15 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.2, 151.8, 149.0, 144.8, 140.4, 132.0, 128.5, 126.9, 125.7, 123.7, 120.9, 120.8, 120.8,

117.6, 114.3, 65.4, 62.7, 49.7, 37.0, 28.1, 14.9; MS (APCI) *m/z* 434 $(M + H)^+$; Anal. Calcd for $C_{23}H_{27}N_7O_2$: C, 63.72; H, 6.28; N, 22.62; Found: C, 63.45; H, 6.04; N, 22.28.

Example 16

N^1-Isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A suspension of *N'*-(3-aminoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (6.50 g, 23.7 mmol) in 100 mL of toluene was treated with trimethyl orthobutyrate (4.18 mL, 26.1 mmol) and pyridine hydrochloride (0.14 g, 1.2 mmol) and heated to 130 °C under an atmosphere of nitrogen. After 18 h, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in 150 mL $CHCl_3$, washed with water (2 X 50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 7.23 g of *tert*-butyl (2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate as an orange foam.

Part B

A solution of *tert*-butyl (2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (7.23 g, 22.2 mmol) in 40 mL of ethanol was treated with HCl (37 mL, 111 mmol, 3 M in ethanol) and heated to reflux. After 1 h, the reaction mixture was cooled to ambient temperature, diluted with 80 mL of diethyl ether, and cooled in an ice water bath. The HCl salt of the product was collected by vacuum filtration and rinsed with diethyl ether until the filtrate ran clear. The dried HCl salt was dissolved in 75 mL of water and treated with 50% NaOH solution until the pH of the water was 12-13. The free base of the product precipitated out and was triturated in the basic water for 30 min while being cooled in an ice water bath. The solid was collected by vacuum filtration and dried under vacuum to give 4.64 g of 2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a tan granular solid.

Part C

A solution of 2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (4.64 g, 20.5 mmol) in 60 mL of acetonitrile and 15 mL of glacial acetic acid was treated with 2,2-dimethoxypropane (12.6 mL, 103 mmol) and heated to 100 °C under an atmosphere of nitrogen. After 6 d, the reaction mixture was concentrated under reduced pressure to yield a brown oil. The oil was dissolved in 100 mL of $CHCl_3$ and washed with 10% Na_2CO_3 (2 X 25 mL), water (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 4.30 g of *N*-isopropylidene-(2-propyl-1*H*-imidazo[4,5-c]quinolin-1-yl)amine as a brown oil.

Part D

A solution of *N*-isopropylidene-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (4.30 g, 16.1 mmol) in 100 mL of methanol was cooled in an ice water bath. The solution was treated with sodium borohydride (3.05 g, 80.7 mmol) over 5 min. The reaction mixture was allowed to warm to ambient temperature. After 2.5, the reaction was quenched by addition of 15 mL of saturated NH_4Cl solution. The mixture was concentrated under reduced pressure to yield a light brown solid. The solid was partitioned between 100 mL $CHCl_3$ and 25 mL of saturated $NaHCO_3$ solution and then separated. The organic portion was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown solid. The solid was purified by chromatography (SiO_2, 97:2.5:0.5 $CHCl_3$:MeOH:NH_4OH) to give 2.48 g of *N*-isopropyl-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine as a tan solid.

Part E

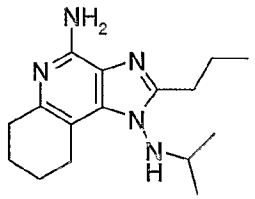
A solution of *N*-isopropyl-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)amine (2.48 g, 9.24 mmol) in 75 mL of chloroform was cooled in a cold water bath. The solution was treated with MCPBA (3.32 g, 11.6 mmol) over 6 min. The reaction was allowed to come to ambient temperature. After 1.5 h, TLC showed complete conversion to the 5-*N*-oxide intermediate. The reaction mixture was again cooled in a cold water bath and then treated with concentrated ammonium hydroxide solution (30 mL, 30%) and stirred rapidly. The reaction mixture was treated with *p*-toluenesulfonyl chloride (1.85 g, 9.70 mmol) over 5 min. The reaction was allowed to come to ambient temperature. After 30 min, the

reaction mixture was diluted with 50 mL of chloroform and 30 mL of water and the phases were separated. The organic portion was washed with 5% Na_2CO_3 solution (30 mL), water (30 mL) and brine (30 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown foam. The material was purified by chromatography (SiO_2, 97:3 $CHCl_3$:MeOH) and recrystallized from EtOAc to yield 1.39 g of N^1-isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as amber crystals.

mp 181–184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 8.1 Hz, 1 H), 7.57 (d, J = 8.3 Hz, 1 H), 7.41-7.35 (m, 1 H), 7.23-7.18 (m, 1 H), 6.95 (d, J = 1.6 Hz, 1 H), 6.48 (s, 2 H), 3.52-3.45 (m, 1 H), 2.98-2.85 (m, 2 H), 1.91-1.79 (m, 2 H), 1.03-0.98 (m, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.5, 152.0, 144.9, 132.6, 126.8, 126.1, 124.2, 121.2, 120.9, 115.0, 51.2, 28.2, 21.1, 20.6, 14.3; MS (APCI) *m/z* 284 $(M + H)^+$; Anal. Calcd for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71; Found: C, 67.66; H, 7.39; N, 24.66.

Example 17

N^1-Isopropyl-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



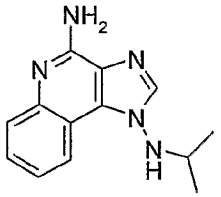
Part A

A solution of N^1-isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.59 g, 2.1 mmol) in 15 mL of trifluoroacetic acid was treated with platinum(IV) oxide (0.55 g, 2.4 mmol) and shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 6 days, the reaction mixture was filtered through a pad of CELITE filter agent and rinsed with a mixture of 85:15:0.1 $CHCl_3$:MeOH:TFA until the filtrate ran clear. The filtrate was concentrated under reduced pressure to yield a white foam. The material was suspended in water and treated with 50 % NaOH solution until the pH reached 13. A white solid precipitated and was triturated in the basic mixture for 1 h. The white solid was collected by vacuum filtration. The solid was purified by chromatography (SiO_2, 95:5:0.1 $CHCl_3$:MeOH:NH_4OH) to yield 0.23 g of N^1-isopropyl-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as a white solid.

mp 162–164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.34 (s, 1 H), 5.64 (s, 2 H), 3.38-3.23 (m, 2 H), 2.85-2.79 (m, 3 H), 2.78-2.71 (m, 2 H), 1.84-1.71 (m, 6 H), 0.99-0.86 (m, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.4, 149.3, 146.1, 137.9, 122.8, 105.7, 52.4, 32.5, 28.4, 23.3, 23.1, 22.9, 21.0, 20.7, 14.3; MS (APCI) *m/z* 288 $(M + H)^+$; Anal. Calcd for $C_{16}H_{25}N_5$: C, 66.87; H, 8.77; N, 24.37; Found: C, 66.65; H, 8.90; N, 24.08.

Example 18

N^1-Isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A suspension of *N'*-(3-aminoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (6.50 g, 23.7 mmol) in 100 mL of toluene was treated with triethyl orthoformate (8.68 mL, 52.2 mmol) and pyridine hydrochloride (0.14 g, 1.2 mmol) and heated to 130 °C under an atmosphere of nitrogen. After 23 h, the reaction mixture was concentrated under reduced pressure to yield a red/brown oil. The oil was dissolved in $CHCl_3$ (150 mL) and washed with water (2 X 50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 6.74 of *tert*-butyl *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate as a red/orange oil.

Part B

A solution of *tert*-butyl *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)carbamate (6.74 g, 23.7 mmol) in 40 mL of ethanol was treated with 40 mL of HCl (40 mL, 119 mmol, 3 M in ethanol) and heated to reflux. After 1 h, the reaction mixture was cooled to ambient temperature, diluted with 80 mL of diethyl ether, and cooled in an ice water bath which precipitated a tan solid. The HCl salt of the product was collected by vacuum filtration and rinsed with diethyl ether until the filtrate ran clear. The dried HCl salt was dissolved in 75 mL of water and made basic by addition of 50% NaOH solution until the pH of the water was 12-13. The free base of the product precipitated out and was triturated in the basic water for 30 min while being cooled in an ice water bath. The solid was collected by

vacuum filtration and dried under vacuum to give 2.86 g of 1*H*-imidazo[4,5-*c*]quinolin-1-amine as a tan granular solid.

Part C

A solution of 1*H*-imidazo[4,5-*c*]quinolin-1-amine (2.86 g, 15.5 mmol) in 60 mL of acetonitrile and 15 mL of glacial acetic acid was treated with 2,2-dimethoxypropane (9.53 mL, 77.5 mmol) and heated to 100 °C under an atmosphere of nitrogen. After 18 h, the reaction mixture was concentrated under reduced pressure to give a brown oil. The oil was dissolved in 100 mL of $CHCl_3$ and washed with 5% Na_2CO_3 solution (2 X 30 mL), water (30 mL) and brine (30 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 3.48 g of *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine as a brown oil.

Part D

A solution of *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine (3.48 g, 15.5 mmol) in 75 mL of methanol was cooled in an ice water bath. The solution was treated over 5 min with sodium borohydride (2.94 g, 77.6 mmol). After 1 h, the reaction mixture was quenched with 20 mL of saturated NH_4Cl solution and then concentrated under reduced pressure to yield a brown soild. The solid was partitioned between 80 mL $CHCl_3$ and 20 mL saturated $NaHCO_3$ solution and the phases were separated. The organic portion was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown solid. The solid was purified by chromatography (SiO_2, 95:5:0.5 $CHCl_3$:MeOH:NH_4OH) to give 1.28 g of *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine as a tan foam.

Part E

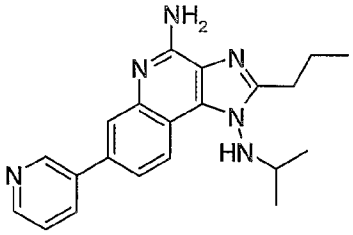
A solution of *N*-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (1.36 g, 5.66 mmol) in 50 mL of chloroform was cooled in a cold water bath. The solution was treated with MCPBA (2.03 g, 7.07 mmol) over 5 min and then allowed to warm to ambient temperature. After 1 h, TLC showed complete conversion to the intermediate 5-*N*-oxide. The reaction mixture was again cooled with a cold water bath. The solution was treated with concentrated ammonium hydroxide solution (25 mL, 30%) and stirred rapidly to

homogenize. The reaction mixture was treated with *p*-toluenesulfonyl chloride (1.13 g, 5.94 g) over 5 min and allowed to warm to ambient temperature. After 30 min, the reaction mixture was diluted with 50 mL of $CHCl_3$ and 25 mL of water. An undissolved solid between the phases was filtered off, saved, and the phases were separated. The organic portion was washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL). The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a tan/orange solid. A high-performance liquid chromatography (HPLC) analysis of the filtered solid matched that of the solid from the concentrated organic extracts. The combined solid was recrystallized twice from MeOH to give 1.18 g of N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as an off-white solid.

mp dec. > 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (dd, J = 8.1, 1.1 Hz, 1 H), 8.23 (s, 1 H), 7.56 (d, J = 7.6 Hz, 1 H), 7.43-7.37 (m, 1 H), 7.23-7.18 (m, 1 H), 7.04 (d, J = 3.4 Hz, 1 H), 6.58 (s, 2 H), 3.57-3.47 (m, 1 H), 1.03 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.4, 145.3, 132.3, 127.3, 126.0, 125.1, 121.5, 121.0, 115.1, 52.6, 20.6; MS (APCI) *m/z* 242 $(M + H)^+$; Anal. Calcd for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.02; Found: C, 63.11; H, 6.30; N, 27.96.

Example 19

N^1-Isopropyl-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A suspension of 7-bromo-4-chloro-3-nitroquinoline (75.00 g, 260.9 mmol) in 350 mL of dichloromethane was cooled to 0 °C under an atmosphere of nitrogen. The suspension was treated with triethylamine (43.25 mL, 326.1 mmol), which dissolved most of the material. A solution of *tert*-butyl carbazate (37.93 g, 287.0 mmol) in 250 mL of dichloromethane was added to the reaction mixture over 20 min. The reaction was allowed to slowly come to ambient temperature. After 15 h, the reaction mixture was

washed with 5% Na_2CO_3 solution (2 X 100 mL) and water (100 mL). The combined aqueous washes were back-extracted with $CHCl_3$ (50 mL). The combined organic portions were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 99.98 g of *N'*-(7-bromo-3-nitroquinolin-4-yl)hydrazine *tert*-butyl carboxylate as a dark red solid.

Part B

A suspension of *N'*-(7-bromo-3-nitroquinolin-4-yl)hydrazine *tert*-butyl carboxylate (50.0 g, 131 mmol) in 320 mL of acetonitrile (MeCN) and 80 mL of methanol was treated with platinum on carbon (5.0 g, 1.3 mmol, 5% w/w) and shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 4 h, the reaction mixture was filtered through a pad of CELITE filter agent and rinsed with portions of MeCN:MeOH (1:1) until the filtrate ran clear. The filtrate was concentrated under reduced pressure to yield 37.1 g of *N'*-(3-amino-7-bromoquinolin-4-yl)hydrazine *tert*-butyl carboxylate as a tan solid.

Part C

A solution of *N'*-(3-amino-7-bromoquinolin-4-yl)hydrazine *tert*-butyl carboxylate (37.1 g, 105 mmol) in 315 mL of toluene was treated with trimethyl orthobutyrate (16.7 mL, 105 mmol) and pyridine hydrochloride (0.12 g, 1.05 mmol). The reaction mixture was heated to reflux under an atmosphere of nitrogen. After 4 h, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to give a brown oil. The oil was dissolved in 300 mL of $CHCl_3$. The solution was washed with 5% Na_2CO_3 (100 mL), water (100 mL) and brine (100 mL). The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a brown foam. The foam was purified by chromatography (SiO_2, 100:0 gradient to 95:5 $CHCl_3$:MeOH) to yield 30.1 g of (7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) *tert*-butyl carbamate as a light brown solid.

Part D

A suspension of (7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) *tert*-butyl carbamate (30.1 g, 74.3 mmol) in 25 mL of ethanol was treated with HCl in ethanol (86.4 mL, 37.1 mmol, 4.3 M) and heated to 100 °C. After 30 min, the reaction mixture was

cooled to ambient temperature and concentrated under reduced pressure to yield a brown solid. The solid was suspended in 100 mL of water, stirred vigorously and treated with 50% NaOH solution until the pH of the liquid rose to 12-13. A brown solid collected around the stir bar. The water was diluted with 200 mL of dichloromethane and the solid was broken apart. The material was triturated in the biphasic mixture overnight. After triturating for 15 h, the mixture was filtered to give the crude free base as a light brown solid. The solid was dried under vacuum to give 17.6 g of 7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a light brown solid.

Part E

A suspension of 7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (17.6 g, 57.7 mmol) in 160 mL of acetonitrile and 40 mL of glacial acetic acid was treated with 2,2-dimethoxypropane (35.5 mL, 288 mmol). The reaction mixture was heated to 100° C under an atmosphere of nitrogen. After 16 h, the reaction was cooled to ambient temperature and concentrated under reduced pressure to yield a brown oil. The oil was dissolved in $CHCl_3$ (200 mL). The $CHCl_3$ solution was washed with saturated $NaHCO_3$ solution (2 X 50 mL), water (50 mL) and brine (50 mL). The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 18.4 g of *N*-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine as a red/brown foam.

Part F

A solution of *N*-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine (18.4 g, 53.3 mmol) in 100 mL of methanol was placed under an atmosphere of nitrogen and cooled in an ice water bath. The solution was treated with sodium borohydride (2.32 g, 61.3 mmol) over 30 min. The reaction mixture was allowed to slowly come to ambient temperature. After 1.5 h, the reaction was quenched by the addition of 25 mL of saturated NH_4Cl solution. The reaction mixture was concentrated under reduced pressure to remove the methanol. The residue was partitioned between chloroform (150 mL) and 10% Na_2CO_3 solution (35 mL), and the phases were separated. The organic portion was washed with another portion of 10% Na_2CO_3 solution (35 mL), water (35 mL) and brine (35 mL). The organic portion was dried over Na_2SO_4, filtered

and concentrated under reduced pressure to yield a brown foam. The foam was purified by chromatography (SiO_2, 97:3 $CHCl_3$:MeOH gradient to 9:1) to give 16.3 g of *N*-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine as a dark tan solid.

Part G

A solution of *N*-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (9.10 g, 26.2 mmol) in 200 mL of chloroform was placed under an atmosphere of nitrogen and cooled in an ice water bath. The solution was treated with MCPBA (8.28 g, 28.8 mmol, 77% max) and allowed to slowly come to ambient temperature. After 2 h, LC/MS and HPLC indicated complete conversion to the 5-*N*-oxide intermediate. The reaction mixture was again cooled in an ice water bath. The reaction mixture was treated with ammonium hydroxide solution (50 mL, 30%) and stirred vigorously. The mixture was treated with *p*-toluenesulfonyl chloride (5.24 g, 27.5 mmol) and allowed to come to ambient temperature. After 30 min, the reaction was diluted with 50 mL of water, and the phases were separated. The organic portion was washed with water (75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light brown solid. The solid was purified by chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) and then recrystallized from acetonitrile to give 4.52 g of 7-bromo-N^1-isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as off white crystals. mp 226–228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 8.7 Hz, 1 H), 7.71 (d, J = 2.1 Hz, 1 H), 7.36 (dd, J = 8.7, 2.1 Hz, 1 H), 6.99 (d, J = 1.7 Hz, 1 H), 6.73 (s, 2 H), 3.53-3.40 (m, 1 H), 2.90 (s, 2 H), 1.93-1.80 (m, 2 H), 1.05-1.00 (m, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.9, 152.9, 146.3, 132.5, 127.8, 124.2, 123.5, 123.1, 119.7, 114.0, 79.5, 51.4, 28.2, 21.1, 20.6, 14.3; MS (APCI) *m/z* 362, 364 $(M + H)^+$; Anal. Calcd for $C_{16}H_{20}BrN_5 \cdot 0.25H_2O$: C, 52.40; H, 5.63; N, 19.09; Found: C, 52.03; H, 5.42; N, 19.14.

Part H

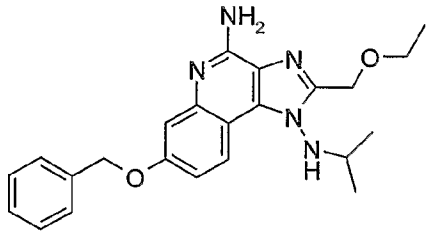
A suspension of 7-bromo-N^1-isopropyl-2-propyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (1.00 g, 2.76 mmol) in 20 mL of 1-propanol was treated with pyridine-3-boronic acid 1,3-propane diol cyclic ester (0.540 g, 3.31 mmol). The head-space of the reaction flask was purged and back-filled with nitrogen (3X). The reaction mixture was then treated with triphenylphosphine (11 mg, 0.041 mmol), sodium carbonate (1.66 mL, 3.31

mmol, 2 M solution in water), water (2 mL) and palladium(II) acetate (3.1 mg, 0.014 mmol). Again the head-space of the reaction flask was purged and back-filled with nitrogen (3X). The reaction was heated to 100° C. After 17 h, the reaction was cooled to ambient temperature and concentrated under reduced pressure to yield a brown solid. The solid was dissolved and partitioned between 15 mL of water and 15 mL of chloroform and then separated. The aqueous portion was extracted with chloroform (2 X 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a tan solid. The solid was purified by chromatography (SiO_2, 95:5 $CHCl_3$:MeOH) and recrystallized from acetonitrile to give 0.515 g of N^1-isopropyl-2-propyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as white crystals.

mp 218–219 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (d, J = 1.7 Hz, 1 H), 8.60-8.57 (m, 2 H), 8.19-8.16 (m, 1 H), 7.88 (d, J = 1.9 Hz, 1 H), 7.61 (dd, J = 8.5, 1.9 Hz, 1 H), 7.53-7.49 (m, 1 H), 7.04 (s, 1 H), 6.59 (s, 2 H), 3.57-3.49 (m, 1 H), 2.92-2.87 (m, 2 H), 1.94-1.82 (m, 2 H), 1.06-1.01 (m, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.8, 152.5, 148.6, 148.1, 145.4, 136.2, 135.4, 134.5, 132.5, 124.5, 124.3, 123.9, 122.2, 119.6, 114.7, 51.3, 28.2, 21.1, 20.6; MS (APCI) *m/z* 361 $(M + H)^+$; Anal. Calcd for $C_{21}H_{24}N_6$: C, 69.97; H, 6.71; N, 23.31; Found: C, 69.78; H, 6.55; N, 23.51.

Example 20

7-Benzyloxy-2-ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine



Part A

A mixture of triethyl orthoformate (92 mL, 0.55 mol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (75.3 g, 0.522 mol) (Meldrum's acid) was heated at 55 °C for 90 minutes and then cooled to 45 °C. A solution of 3-benzyloxyaniline (100.2 g, 0.5029 mol) in methanol (200 mL) was slowly added to the reaction over a period 45 minutes while maintaining the reaction temperature below 50 °C. The reaction was then heated at 45 °C

for one hour, allowed to cool to room temperature, and stirred overnight. The reaction mixture was cooled to 1 °C, and the product was isolated by filtration and washed with cold ethanol (~400 mL) until the filtrate was colorless. 5-{[(3-Benzyloxy)phenylimino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (170.65 g) was isolated as a tan, powdery solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.21 (d, J = 14.2 Hz, 1H), 8.61 (d, J = 14.2 Hz, 1H), 7.49-7.30 (m, 7H), 7.12 (dd, J = 8.1, 1.96 Hz, 1H), 6.91 (dd, J = 8.4, 2.1 Hz, 1H), 5.16 (s, 2H), 1.68 (s, 6H).

Part B

A mixture of 5-{[(3-benzyloxy)phenylimino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (170.65 g, 0.483 mol) and DOWTHERM A heat transfer fluid (800 mL) was heated to 100 °C and then slowly added to a flask containing DOWTHERM A heat transfer fluid (1.3 L, heated at 210 °C) over a period of 40 minutes. During the addition, the reaction temperature was not allowed to fall below 207 °C. Following the addition, the reaction was stirred at 210 °C for one hour, and then allowed to cool to ambient temperature. A precipitate formed, which was isolated by filtration, washed with diethyl ether (1.7 L) and acetone (0.5 L), and dried in an oven to provide 76.5 g of 7-benzyloxyquinolin-4-ol as a tan powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.99 (dd, J = 7.4, 2.4 Hz, 1H), 7.79 (d, J = 7.4 Hz, 1H), 7.50-7.32 (m, 5H), 7.00 (s, 1H), 6.98 (dd, J = 7.4, 2.5 Hz, 1H), 5.93 (d, J = 7.5 Hz, 1H), 5.20 (s, 2H).

Part C

A mixture of 7-benzyloxyquinolin-4-ol (71.47 g, 0.2844 mol) and propionic acid (700 mL) was heated to 125 °C with vigorous stirring. Nitric acid (23.11 mL of 16 M) was slowly added over a period of 30 minutes while maintaining the reaction temperature between 121 °C and 125 °C. After the addition, the reaction was stirred at 125 °C for 1 hour then allowed to cool to ambient temperature. The resulting solid was isolated by filtration, washed with water, and dried in an oven for 1.5 days to provide 69.13 g of 7-benzyloxy-3-nitroquinolin-4-ol as a grayish powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.77 (s, 1H), 9.12 (s, 1H), 8.17 (dd, J = 6.3, 3.3 Hz, 1H), 7.51-7.33 (m, 5H), 7.21-7.17 (m, 2H), 5.25 (s, 2H).

Part D

A suspension of 7-benzyloxy-3-nitroquinolin-4-ol (75.0 g, 253 mmol), which was made in a separate run, in 500 mL of *N,N*-dimethylformamide was placed under an atmosphere of nitrogen. The suspension was treated with phosphorous oxychloride (27.8 mL, 304 mmol) dropwise over 1.5 h. After 18 h, the reaction mixture was cooled to 0 °C and then poured into 1 L of ice water. The mixture was stirred until the ice had melted. A tan/yellow precipitate was collected by vacuum filtration. The solid was dissolved in dichloromethane (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 71.7 g of 7-benzyloxy-4-chloro-3-nitro-quinoline as an orange solid.

Part E

A solution of *tert*-butyl carbazate (33.1 g, 251 mmol) in 150 mL of dichloromethane was treated with triethylamine (66.5 mL, 502 mmol). The solution was placed under an atmosphere of nitrogen and cooled in a cold-water bath. The solution was treated with a solution of 7-benzyloxy-4-chloro-3-nitroquinoline (71.7 g, 228 mmol) in 350 mL of dichloromethane over 1 h. The reaction was stirred and allowed to warm to ambient temperature. After 15 h, the reaction was diluted with 200 mL of water and 250 mL of $CHCl_3$ and the phases were separated. The organic portion was washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield an orange solid. The solid was recrystallized from dichloromethane to yield 53.5 g of *N'*-(7-benzyloxy-3-nitroquinolin-4-yl)hydrazine *tert*-butyl carboxylate as yellow crystals.

Part F

A solution of *N'*-(7-benzyloxy-3-nitroquinolin-4-yl)hydrazine *tert*-butyl carboxylate (20.00 g, 48.73 mmol) in 200 mL of methanol and 200 mL of acetonitrile was treated with platinum on carbon (2.00 g, 0.51 mmol) and shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 17 h, the mixture was filtered through a pad of CELITE filter agent and rinsed with MeOH:MeCN (1:1) until the filtrate ran clear. The filtrate was

concentrated under reduced pressure to yield 18.21 g of *N'*-(3-amino-7-benzyloxyquinolin-4-yl)hydrazine *tert*-butyl carboxylate as a red/orange solid.

Part G

A suspension of *N'*-(3-amino-7-benzyloxyquinolin-4-yl)hydrazine *tert*-butyl carboxylate (29.6 g, 77.8 mmol) in 250 mL of 1,2-dichloroethane was placed under an atmosphere of nitrogen. The mixture was treated with triethylamine (30.9 mL, 233 mmol). The mixture was then treated dropwise with ethoxyacetyl chloride (10.5 g, 85.6 mmol). After 2 h, the reaction was concentrated under reduced pressure to give a brown oil. The oil was dissolved in 200 mL of 1-butanol and treated with pyridinium *p*-toluenesulfonate (0.25 g, 1.0 mmol). The mixture was heated to 135 °C under an atmosphere of nitrogen. After 20 h, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to give a brown oil. The oil was dissolved in 250 mL of $CHCl_3$ and washed with saturated $NaHCO_3$ solution (75 mL), water (75 mL) and brine (75 mL). The organic portion was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give an orange/brown oil. The oil was purified by chromatography (SiO_2, 9:1 $CHCl_3$:MeOH) to yield 14.4 g of (7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)*tert*-butyl carbamate as an orange/brown foam.

Part H

A suspension of (7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)*tert*-butyl carbamate (14.4 g, 32.1 mmol) in 100 mL of ethanol was treated with HCl in ethanol (38 mL, 160 mmol, 4.3 M). The mixture was heated to 100 °C under an atmosphere of nitrogen. After 2 h, the reaction mixture was cooled to ambient temperature at which point a solid precipitated from solution. The mixture was diluted with 100 mL of diethyl ether and the solid was triturated for 15 min. The solid was collected by vacuum filtration and washed with several portions of diethyl ether. The solid was dried under vacuum for 2 h. The dry solid was suspended in 150 mL of water and treated with 50% NaOH solution until the pH of the liquid was 12. A brown solid precipitated. The mixture was diluted with 200 mL of CH_2Cl_2 and stirred until the solid dissolved. The layers were then separated. The aqueous portion was extracted with

CH_2Cl_2 (2 X 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 6.91 g of 7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine as a dark tan solid.

Part I

A suspension of 7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-amine (6.91 g, 19.8 mmol) in 55 mL of acetonitrile was treated with 2,2-dimethoxypropane (12.2 mL, 99.2 mmol) and 14 mL of glacial acetic acid. The reaction mixture was heated to 100 °C under an atmosphere of nitrogen. After 22 h, the reaction was cooled to ambient temperature and concentrated under reduced pressure to yield a brown oil. The oil was dissolved in 125 mL of $CHCl_3$ and washed with saturated $NaHCO_3$ solution (2 X 30 mL) and water (30 mL). The combined aqueous washes were back-extracted with $CHCl_3$ (25 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 7.69 g of *N*-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine as a brown solid.

Part J

A solution of *N*-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylideneamine (7.69 g, 19.8 mmol) in 50 mL of methanol was cooled to 0 °C. The solution was treated with sodium borohydride (1.12 g, 29.7 mmol) over 10 min. The reaction was allowed to slowly come to ambient temperature. After 2 h, the reaction was quenched with 15 mL of saturated NH_4Cl solution and concentrated under reduced pressure to yield a tan solid residue. The solid was dissolved in 100 mL of $CHCl_3$ and 25 mL of saturated K_2CO_3 solution then separated. The organic portion was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated to yield a brown oil. The oil was purified by chromatography (SiO_2, 98:2 $CHCl_3$:MeOH) to yield 6.63 g of *N*-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine as a tan foam.

Part K

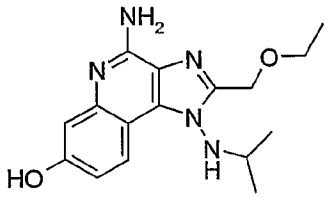
A solution of *N*-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)isopropylamine (6.63 g, 17.0 mmol) in 90 mL of $CHCl_3$ was treated with MPCBA (6.29

g, 25.5 mmol, 70%). After 3 h, HPLC and LC/MS indicated complete conversion to the intermediate 5-*N*-oxide. The reaction mixture was then treated with concentrated ammonium hydroxide solution (30 mL, 30%). The biphasic reaction mixture was stirred vigorously while *p*-toluenesulfonyl chloride (3.40 g, 17.9 mmol) was added. After 45 min, LC/MS indicated complete conversion to the 4-amine. The reaction mixture was diluted with 30 mL of water and 45 mL of $CHCl_3$ and separated. The organic portion was washed with 10% Na_2CO_3 solution (50 mL) and water (50 mL). The combined aqueous portions were then back-extracted with $CHCl_3$ (25 mL). The combined organic portions were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to yield a tan solid. The solid was purified by chromatography (SiO_2, 96:4 $CHCl_3$:MeOH) to give 5.90 g of 7-benzyloxy-2-ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine as a light tan solid.

mp 194–196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (d, J = 8.9 Hz, 1 H), 7.50-7.48 (m, 2 H), 7.43-7.38 (m, 2 H), 7.35-7.30 (m, 1 H), 7.09 (d, J = 2.6 Hz, 1 H), 6.96 (dd, J = 9.0, 2.5 Hz, 1 H), 6.91 (d, J = 1.5 Hz, 1 H), 6.57 (s, 2 H), 5.20 (s, 2 H), 4.72 (s, 2 H), 3.64-3.57 (m, 3 H), 1.15 (t, J = 7.0 Hz, 3 H), 1.01 (d, J = 6.1 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.9, 152.6, 149.4, 147.1, 137.7, 133.7, 128.8, 128.1, 128.0, 122.7, 111.8, 109.2, 108.4, 69.5, 65.8, 63.0, 51.6, 20.6, 15.3; MS (APCI) *m/z* 406 $(M + H)^+$; Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27; Found: C, 68.15; H, 6.91; N, 17.24.

Example 21

4-Amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-*c*]quinolin-7-ol

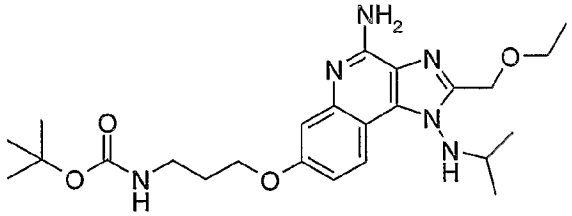


Part A

A solution of 7-benzyloxy-2-ethoxymethyl-N^1-isopropyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (1.67 g, 4.12 mmol) in 25 mL of toluene and 25 mL of methanol was treated with palladium on carbon (0.44 g, 0.42 mmol, 10% w/w). The mixture was shaken under an atmosphere of hydrogen (3.8 x 10^5 Pa). After 16 h, the reaction was filtered through a pad of CELITE filter agent and rinsed with solvent until the filtrate ran clear. The filtrate was concentrated under reduced pressure to provide a white solid. Purification by chromatography (SiO_2, 3:1 $CHCl_3$:(80:18:2 $CHCl_3$:MeOH:NH_4OH) gradient to 1:1) gave 0.50 g of 4-amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-c]quinolin-7-ol as a white solid. MS (APCI) *m/z* 316 $(M + H)^+$.

Example 22

[3-(4-Amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-c]quinolin-7-yloxy)propyl] *tert*-butyl carbamate



Part A

A solution of di-*tert*-butyl dicarbonate (19.05 g, 87.29 mmol) in tetrahydrofuran (20 mL) was added dropwise to a mixture of 3-amino-1-propanol (6.55 g, 87.2 mmol), tetrahydrofuran (50 mL), and 10% aqueous sodium hydroxide (35 mL). The reaction was stirred for 16 hours. The tetrahydrofuran was removed under reduced pressure, and the residue was adjusted to pH 3 with the slow addition of 15% aqueous potassium hydrogen sulfate. The mixture was extracted with ethyl acetate (3 x), and the combined organic

fractions were washed sequentially with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to provide 16.6 g of *tert*-butyl 3-hydroxypropylcarbamate as a colorless oil containing some residual ethyl acetate.

Part B

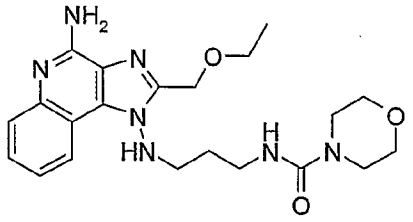
Iodine (21.1 g, 83.1 mmol) was added in three portions to a solution of triphenylphosphine (19.83 g, 75.6 mmol) and imidazole (5.15 g, 75.6 mmol) in dichloromethane (300 mL). The resulting reddish-brown solution with a white precipitate was stirred until all of the iodine had dissolved. A solution of *tert*-butyl 3-hydroxypropylcarbamate (13.25 g, 75.61 mmol) in dichloromethane (150 mL) was added over a period of 45 minutes, and the reaction was stirred for 16 hours at ambient temperature. The reaction mixture was poured into saturated aqueous sodium thiosulfate and stirred until solution became colorless. The organic layer was separated and washed sequentially with saturated aqueous sodium thiosulfate, water, and brine; dried over anhydrous magnesium sulfate; filtered; and concentrated under reduced pressure to a pale yellow oil. The oil was purified by flash column chromatography (eluting with 80:20 hexanes:ethyl acetate) to a pale yellow oil which slowly crystallizes upon standing to afford 16.2 g of *tert*-butyl 3-iodopropylcarbamate as a yellow solid.

Part C

A solution of 4-amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-c]quinolin-7-ol (0.11 g, 0.35 mmol) in 10 mL of *N,N*-dimethylformamide was placed under an atmosphere of nitrogen and was treated with cesium carbonate (0.23 g, 0.70 mmol). After 5 min of stirring the mixture was treated with *tert*-butyl 3-iodopropylcarbamate (0.12 g, 0.35 mmol) and heated to 65 °C. After 60 h, the reaction mixture was cooled to ambient temperature and then poured into 100 mL of ice water which resulted in a cloudy suspension. The mixture was extracted with $CHCl_3$ (5 X 25 mL). The combined organic extracts were then washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a tan oil. Chromatography (95:5 $CHCl_3$:(80:18:2 $CHCl_3$:MeOH:NH_4OH) gradient to 1:1 gave 0.040 g of [3-(4-amino-2-ethoxymethyl-1-isopropylamino-1*H*-imidazo[4,5-c]quinolin-7-yloxy)propyl] *tert*-butyl carbamate as a light tan solid. LC/MS (APCI) *m/z* 473 $(M+H)^+$.

Example 23

[3-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-ylamino)propyl]morpholine-4-carboxamide

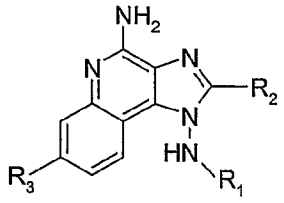


A solution of N^1-(3-aminopropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-1,4-diamine (0.500 g, 1.59 mmol) in 10 mL of CH_2Cl_2 was treated with triethylamine (0.443 mL, 3.34 mmol) under an atmosphere of nitrogen and cooled to 0 °C. The reaction mixture was treated dropwise with 4-morpholinecarbonyl chloride (0.065 mL, 0.835 mmol) and allowed to slowly come to ambient temperature. After 60 h, the reaction mixture was quenched with 10% Na_2CO_3 solution, diluted with $CHCl_3$ and the phases were separated. The organic portion was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a light yellow solid. Chromatography (SiO_2, 9:1 $CHCl_3$:(80:18:2 $CHCl_3$:MeOH:NH_4OH) gradient to 1:1) gave a glassy solid. The solid was triturated with diethyl ether and filtered to give 0.046 g of [3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-ylamino)propyl]morpholine-4-carboxamide as a white solid.

mp 158–160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 7.9 Hz, 1 H), 7.58 (d, J = 8.1 Hz, 1 H), 7.46-7.41 (m, 1 H), 7.26-7.21 (m, 1 H), 6.96 (t, J = 5.5 Hz, 1 H), 6.60 (s, 2 H), 6.53 (t, J = 5.1 Hz, 1 H), 4.75 (s, 2 H), 3.61 (q, J = 7.0 Hz, 2 H), 3.50 (t, J = 4.7 Hz, 4 H), 3.22-3.15 (m, 8 H), 1.72 (p, J = 6.9 Hz, 2 H), 1.17 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.0, 152.3, 149.5, 145.3, 132.4, 127.4, 126.1, 124.2, 121.2, 114.7, 66.3, 65.8, 63.1, 50.2, 44.1, 38.3, 28.5, 15.4; MS (APCI) m/z 428 $(M + H)^+$; Anal. Calcd for $C_{21}H_{29}N_7O_3$: C, 59.00; H, 6.84; N, 22.93; Found: C, 58.76; H, 7.04; N, 22.82.

Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (I-1d) and the following R_1, R_2, and R_3 substituents, wherein each line of the table represents a specific compound.



I-1d

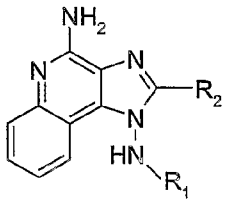
R_1	R_2	R_3
isopropyl	hydrogen	pyridin-3-yl
isopropyl	hydrogen	benzyloxy
isopropyl	hydrogen	2-methanesulfonylaminoethoxy
isopropyl	hydrogen	3-methanesulfonylaminopropoxy
isopropyl	hydrogen	2-(pyridin-3-yl)ethyl
isopropyl	methyl	pyridin-3-yl
isopropyl	methyl	benzyloxy
isopropyl	methyl	2-methanesulfonylaminoethoxy
isopropyl	methyl	3-methanesulfonylaminopropoxy
isopropyl	methyl	2-(pyridin-3-yl)ethyl
isopropyl	propyl	pyridin-3-yl
isopropyl	propyl	benzyloxy
isopropyl	propyl	2-methanesulfonylaminoethoxy
isopropyl	propyl	3-methanesulfonylaminopropoxy
isopropyl	propyl	2-(pyridin-3-yl)ethyl
isopropyl	butyl	pyridin-3-yl
isopropyl	butyl	benzyloxy
isopropyl	butyl	2-methanesulfonylaminoethoxy
isopropyl	butyl	3-methanesulfonylaminopropoxy
isopropyl	butyl	2-(pyridin-3-yl)ethyl
isopropyl	2-methoxyethyl	pyridin-3-yl
isopropyl	2-methoxyethyl	benzyloxy
isopropyl	2-methoxyethyl	2-methanesulfonylaminoethoxy
isopropyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
isopropyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
isopropyl	ethoxymethyl	pyridin-3-yl
isopropyl	ethoxymethyl	benzyloxy
isopropyl	ethoxymethyl	2-methanesulfonylaminoethoxy
isopropyl	ethoxymethyl	3-methanesulfonylaminopropoxy
isopropyl	ethoxymethyl	2-(pyridin-3-yl)ethyl
benzyl	hydrogen	pyridin-3-yl
benzyl	hydrogen	benzyloxy
benzyl	hydrogen	2-methanesulfonylaminoethoxy

benzyl	hydrogen	3-methanesulfonylaminopropoxy
benzyl	hydrogen	2-(pyridin-3-yl)ethyl
benzyl	methyl	pyridin-3-yl
benzyl	methyl	benzyloxy
benzyl	methyl	2-methanesulfonylaminoethoxy
benzyl	methyl	3-methanesulfonylaminopropoxy
benzyl	methyl	2-(pyridin-3-yl)ethyl
benzyl	propyl	pyridin-3-yl
benzyl	propyl	benzyloxy
benzyl	propyl	2-methanesulfonylaminoethoxy
benzyl	propyl	3-methanesulfonylaminopropoxy
benzyl	propyl	2-(pyridin-3-yl)ethyl
benzyl	butyl	pyridin-3-yl
benzyl	butyl	benzyloxy
benzyl	butyl	2-methanesulfonylaminoethoxy
benzyl	butyl	3-methanesulfonylaminopropoxy
benzyl	butyl	2-(pyridin-3-yl)ethyl
benzyl	2-methoxyethyl	pyridin-3-yl
benzyl	2-methoxyethyl	benzyloxy
benzyl	2-methoxyethyl	2-methanesulfonylaminoethoxy
benzyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
benzyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
benzyl	ethoxymethyl	pyridin-3-yl
benzyl	ethoxymethyl	benzyloxy
benzyl	ethoxymethyl	2-methanesulfonylaminoethoxy
benzyl	ethoxymethyl	3-methanesulfonylaminopropoxy
benzyl	ethoxymethyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	hydrogen	pyridin-3-yl
3-phenylpropyl	hydrogen	benzyloxy
3-phenylpropyl	hydrogen	2-methanesulfonylaminoethoxy
3-phenylpropyl	hydrogen	3-methanesulfonylaminopropoxy
3-phenylpropyl	hydrogen	2-(pyridin-3-yl)ethyl
3-phenylpropyl	methyl	pyridin-3-yl
3-phenylpropyl	methyl	benzyloxy
3-phenylpropyl	methyl	2-methanesulfonylaminoethoxy
3-phenylpropyl	methyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	methyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	propyl	pyridin-3-yl
3-phenylpropyl	propyl	benzyloxy
3-phenylpropyl	propyl	2-methanesulfonylaminoethoxy
3-phenylpropyl	propyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	propyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	butyl	pyridin-3-yl
3-phenylpropyl	butyl	benzyloxy
3-phenylpropyl	butyl	2-methanesulfonylaminoethoxy
3-phenylpropyl	butyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	butyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	2-methoxyethyl	pyridin-3-yl
3-phenylpropyl	2-methoxyethyl	benzyloxy
3-phenylpropyl	2-methoxyethyl	2-methanesulfonylaminoethoxy

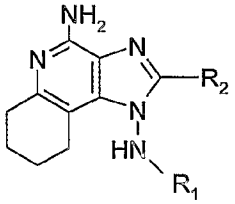
3-phenylpropyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
3-phenylpropyl	ethoxymethyl	pyridin-3-yl
3-phenylpropyl	ethoxymethyl	benzyloxy
3-phenylpropyl	ethoxymethyl	2-methanesulfonylaminoethoxy
3-phenylpropyl	ethoxymethyl	3-methanesulfonylaminopropoxy
3-phenylpropyl	ethoxymethyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	hydrogen	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	hydrogen	benzyloxy
3-[3-(2-propyl)ureido]propyl	hydrogen	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	hydrogen	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	hydrogen	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	methyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	methyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	methyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	methyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	methyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	propyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	propyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	propyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	propyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	propyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	butyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	butyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	butyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	butyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	butyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	pyridin-3-yl
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	benzyloxy
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	2-methanesulfonylaminoethoxy
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	3-methanesulfonylaminopropoxy
3-[3-(2-propyl)ureido]propyl	ethoxymethyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	hydrogen	pyridin-3-yl
3-methanesulfonylaminopropyl	hydrogen	benzyloxy
3-methanesulfonylaminopropyl	hydrogen	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	hydrogen	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	hydrogen	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	methyl	pyridin-3-yl
3-methanesulfonylaminopropyl	methyl	benzyloxy
3-methanesulfonylaminopropyl	methyl	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	methyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	methyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	propyl	pyridin-3-yl
3-methanesulfonylaminopropyl	propyl	benzyloxy
3-methanesulfonylaminopropyl	propyl	2-methanesulfonylaminoethoxy

3-methanesulfonylaminopropyl	propyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	propyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	butyl	pyridin-3-yl
3-methanesulfonylaminopropyl	butyl	benzyloxy
3-methanesulfonylaminopropyl	butyl	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	butyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	butyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	2-methoxyethyl	pyridin-3-yl
3-methanesulfonylaminopropyl	2-methoxyethyl	benzyloxy
3-methanesulfonylaminopropyl	2-methoxyethyl	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	2-methoxyethyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	2-methoxyethyl	2-(pyridin-3-yl)ethyl
3-methanesulfonylaminopropyl	ethoxymethyl	pyridin-3-yl
3-methanesulfonylaminopropyl	ethoxymethyl	benzyloxy
3-methanesulfonylaminopropyl	ethoxymethyl	2-methanesulfonylaminoethoxy
3-methanesulfonylaminopropyl	ethoxymethyl	3-methanesulfonylaminopropoxy
3-methanesulfonylaminopropyl	ethoxymethyl	2-(pyridin-3-yl)ethyl

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (Ii or IIb) and the following R_1 and R_2 substituents, wherein each line of the table is matched with Formula Ii or IIb to represent a specific compound.



Ii



IIb

R_1	R_2
isopropyl	hydrogen
isopropyl	methyl
isopropyl	propyl
isopropyl	butyl
isopropyl	2-methoxyethyl
isopropyl	ethoxymethyl
benzyl	hydrogen
benzyl	methyl
benzyl	propyl
benzyl	butyl
benzyl	2-methoxyethyl
benzyl	ethoxymethyl
3-phenylpropyl	hydrogen
3-phenylpropyl	methyl
3-phenylpropyl	propyl
3-phenylpropyl	butyl

3-phenylpropyl	2-methoxyethyl
3-phenylpropyl	ethoxymethyl
3-[3-(2-propyl)ureido]propyl	hydrogen
3-[3-(2-propyl)ureido]propyl	methyl
3-[3-(2-propyl)ureido]propyl	propyl
3-[3-(2-propyl)ureido]propyl	butyl
3-[3-(2-propyl)ureido]propyl	2-methoxyethyl
3-[3-(2-propyl)ureido]propyl	ethoxymethyl
3-methanesulfonylaminopropyl	hydrogen
3-methanesulfonylaminopropyl	methyl
3-methanesulfonylaminopropyl	propyl
3-methanesulfonylaminopropyl	butyl
3-methanesulfonylaminopropyl	2-methoxyethyl
3-methanesulfonylaminopropyl	ethoxymethyl

CYTOKINE INDUCTION IN HUMAN CELLS

Many compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using the method described below. Particular examples include but are not limited to the compounds of Examples 1-18.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture:

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation:

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation:

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation:

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (~200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA:

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

TNF-α INHIBITION IN MOUSE CELLS

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below.

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor-α (TNF-α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3 x 10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 µL) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3 x 10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5µM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by a dose response assay.

Incubation

A solution of test compound (1µl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 µL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 µL) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1 x 10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 µM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by dose response assay.

Incubation

A solution of test compound (200 µl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 µL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

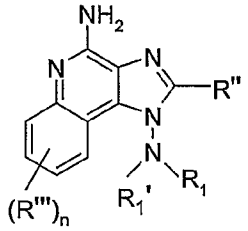
Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource

International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the Formula (I):



I

wherein:

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

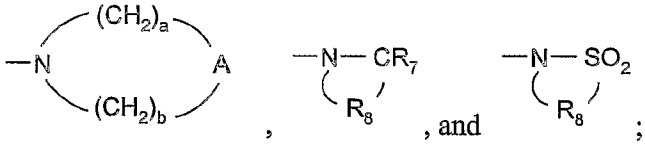
$-X-R_5$,

$-X-N(R_6)-Y-R_4$,

$-X-C(R_7)-N(R_6)-R_4$, and

$-X-O-R_4$;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:

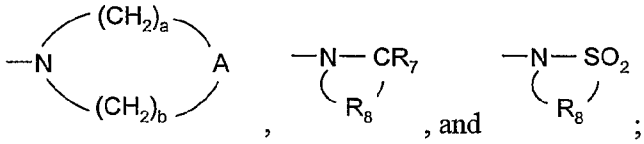


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl

group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

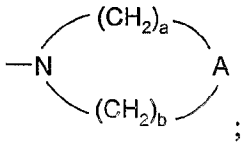
R_7 is selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -$CH(R_6)$-, -O-, -$N(R_6)$-, -$N(Y\text{-}R_4)$-, and -$N(X\text{-}N(R_6)\text{-}Y\text{-}R_4)$-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -$C(R_7)$-, -$C(R_7)$-O-, -$S(O)_2$-, -$S(O)_2\text{-}N(R_6)$-, and -$C(R_7)\text{-}N(R_9)$-; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -$N(R_6)$-, -$N(Y\text{-}R_4)$-, or -$N(X\text{-}N(R_6)\text{-}Y\text{-}R_4)$- then a and b are independently integers from 2 to 4;

each R" is independently hydrogen or a non-interfering substituent;

each R"' is independently a non-interfering substituent; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein the compound induces the biosynthesis of one or more cytokines.

3. The compound or salt of claim 1 wherein R" is selected from the group consisting of:

-hydrogen,
-alkyl,
-alkenyl,
-aryl,
-heteroaryl,
-heterocyclyl,
-alkylene-Z-alkyl,
-alkylene-Z-aryl,
-alkylene-Z-alkenyl, and
-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
-OH,
-halogen,
$-N(R_6)_2$,
$-C(R_7)-N(R_6)_2$,
$-S(O)_2-N(R_6)_2$,
$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,
$-N(R_6)-S(O)_2-C_{1-10}$ alkyl,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
-aryl,
-heteroaryl,
-heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

each R_7 is independently selected from the group consisting of =O and =S; and

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$.

4. The compound or salt of claim 1 wherein:

R''' is R or R_3 when n is 1, R or one R and one R_3 when n is 2, or R when n is 3 to 4;

R is selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

R_3 is selected from the group consisting of:

-Z'-R_4',

-Z'-X'-R_4',

-Z'-X'-Y'-R_4', and

-Z'-X'-R_5';

Z' is a bond or -O-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene, or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_{11})$-,

-$C(R_7)$-,

-$C(R_7)$-O-,

-O-$C(R_7)$-,

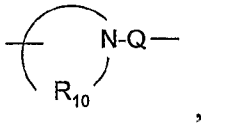
-O-C(O)-O-,

-$N(R_{11})$-Q-,

-$C(R_7)$-$N(R_{11})$-,

-O-$C(R_7)$-$N(R_{11})$-,

-$C(R_7)$-$N(OR_{12})$-,



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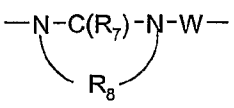

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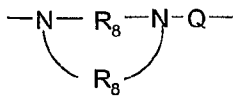
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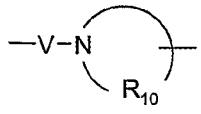
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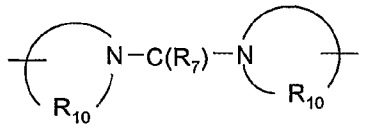
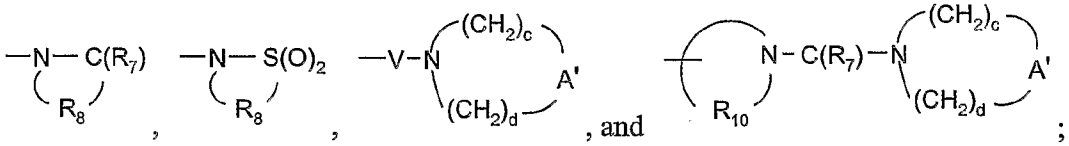

;

R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5' is selected from the group consisting of:


;

each R_7 is independently selected from the group consisting of =O and =S;

each R_8 is independently C_{2-7} alkylene;

R_{10} is C_{3-8} alkylene;

each R_{11} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxyC_{2-10} alkylenyl, and arylC_{1-10} alkylenyl;

R_{12} is selected from the group consisting of hydrogen and alkyl;

A' is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4')-$;

Q is selected from the group consisting of a bond, $-C(R_7)-$, $-C(R_7)-C(R_7)-$,

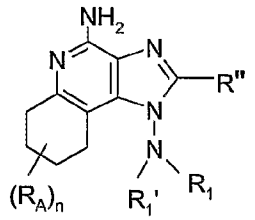
$-S(O)_2-$, $-C(R_7)-N(R_{11})-W-$, $-S(O)_2-N(R_{11})-$, $-C(R_7)-O-$, and $-C(R_7)-N(OR_{12})-$;

V is selected from the group consisting of $-C(R_7)-$, $-O-C(R_7)-$, $-N(R_{11})-C(R_7)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7, and when A' is -O- or $-N(R_4')-$ then c and d are independently integers from 2 to 4.

5. A compound of the Formula (II):



II

wherein:

each R_A is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio,

$-NH_2$,

-NH(alkyl), and

$-N(alkyl)_2$;

n is an integer from 0 to 4;

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

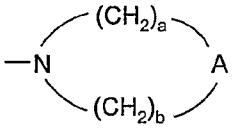
-X-R_5,

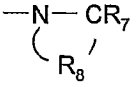
-X-N(R_6)-Y-R_4,

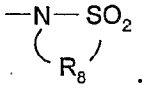
-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



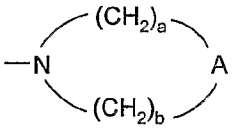
, 

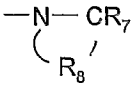
, and 

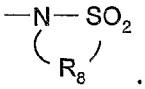
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



, 

, and 

;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

R_7 is selected from the group consisting of =O and =S;

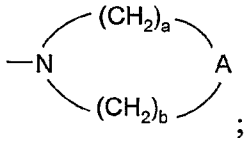
R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-,

$-S(O)_2-N(R_6)-$, and $-C(R_7)-N(R_9)-$; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



;

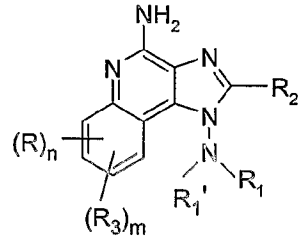
a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4; and

R" is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

6. The compound or salt of claim 5 wherein the compound or salt induces the biosynthesis of one or more cytokines.

7. A compound of the Formula (I-1):



I-1

wherein:

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

$-R_4$,

$-Y-R_4$,

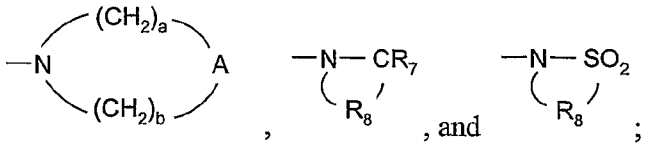
$-X-R_5$,

$-X-N(R_6)-Y-R_4$,

$-X-C(R_7)-N(R_6)-R_4$, and

$-X-O-R_4$;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)-S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_3 is selected from the group consisting of:

-Z'-R_4',

-Z'-X'-R_4',

-Z'-X'-Y'-R_4', and

-Z'-X'-R_5';

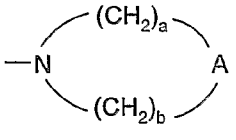
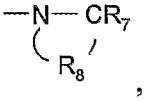
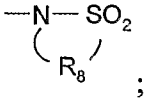
each R is independently selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

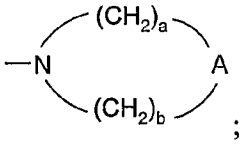
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:


, 
, and 
;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group


;

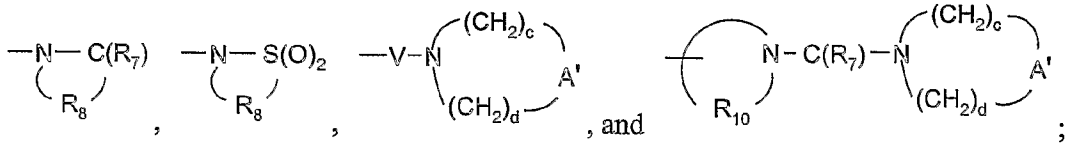
Z is selected from the group consisting of -O- and -$S(O)_{0-2}$-;

A is selected from the group consisting of -$CH(R_6)$-, -O-, -$N(R_6)$-, -$N(Y\text{-}R_4)$-, and -$N(X\text{-}N(R_6)\text{-}Y\text{-}R_4)$-;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -$N(R_6)$-, -$N(Y\text{-}R_4)$-, or -$N(X\text{-}N(R_6)\text{-}Y\text{-}R_4)$- then a and b are independently integers from 2 to 4;

R_4' is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5' is selected from the group consisting of:



;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene, or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_{11})$-,

-$C(R_7)$-,

-$C(R_7)$-O-,

-O-$C(R_7)$-,

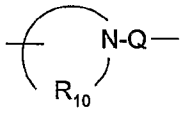
-O-C(O)-O-,

$-N(R_{11})-Q-$,

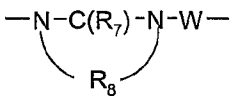
$-C(R_7)-N(R_{11})-$,

$-O-C(R_7)-N(R_{11})-$,

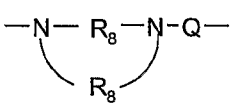
$-C(R_7)-N(OR_{12})-$,



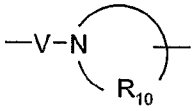
,



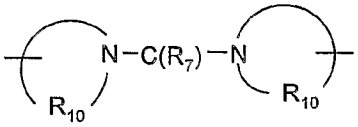
,



,



, and



;

Z' is a bond or -O-;

A' is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4')-$;

Q is selected from the group consisting of a bond, $-C(R_7)-$, $-C(R_7)-C(R_7)-$, $-S(O)_2-$, $-C(R_7)-N(R_{11})-W-$, $-S(O)_2-N(R_{11})-$, $-C(R_7)-O-$, and $-C(R_7)-N(OR_{12})-$;

V is selected from the group consisting of $-C(R_7)-$, $-O-C(R_7)-$, $-N(R_{11})-C(R_7)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

c and d are independently integers from 1 to 6 with the proviso that c + d is ≤ 7, and when A' is -O- or $-N(R_4')-$ then c and d are independently integers from 2 to 4;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

each R_7 is independently selected from the group consisting of =O and =S;

each R_8 is independently C_{2-7} alkylene;

R_{10} is C_{3-8} alkylene;

each R_{11} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxyC_{2-10} alkylenyl, and arylC_{1-10} alkylenyl; and

R_{12} is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

8. The compound or salt according to claim 7 wherein R_1 is selected from the group consisting of $-R_4$, $-Y-R_4$, and $-X-N(R_6)-Y-R_4$ wherein Y is $-C(R_7)-$, $-S(O)_2-$, or $-C(R_7)-N(R_9)-$.

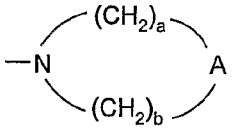
9. The compound or salt according to claim 8 wherein R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl, heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, heterocyclylcarbonylaminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

10. The compound or salt according to claim 9 wherein R_1 is selected from the group consisting of hydrogen, methyl, isopropyl, butyl, 2-methylpropyl, 1-ethylpropyl, 3-methylbutyl, cyclohexyl, benzyl, 3-phenylpropyl, cinnamyl, furan-2-ylmethyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from the group consisting of methanesulfonyl, phenylsulfonyl, benzyl, isopropylaminocarbonyl, morpholine-4-carbonyl, and phenylaminocarbonyl.

11. The compound or salt according to claim 7 wherein R_1' is hydrogen.

12. The compound or salt of claim 7 wherein R_1 and R_1' are each independently alkyl.

13. The compound or salt of claim 7 wherein R_1 and R_1' join to form the group:



14. The compound or salt according to claim 7 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

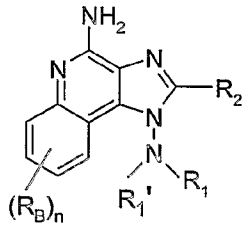
15. The compound or salt according to claim 14 wherein R_2 is selected from the group consisting of hydrogen, methyl, propyl, butyl, 2-methoxyethyl, and ethoxymethyl.

16. The compound or salt according to claim 7 wherein n is 0.

17. The compound or salt according to claim 7 wherein n is 0, and R_3 is selected from the group consisting of -Z'-R_4', -Z'-X'-R_4', and -Z'-X'-Y'-R_4'.

18. The compound or salt according to claim 17 wherein R_3 is selected from the group consisting of 2-(pyridin-3-yl)ethyl, pyridinyl, hydroxymethylpyridinyl, ethoxyphenyl, (morpholine-4-carbonyl)phenyl, 2-(methanesulfonylamino)ethoxy, and benzyloxy.

19. A compound of the Formula (I-2):



I-2

wherein:

R_B is selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

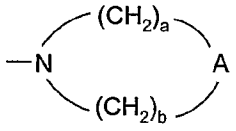
-X-R_5,

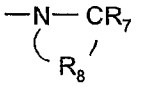
-X-N(R_6)-Y-R_4,

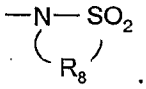
-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



, 

, and 

;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

-N(R_6)$_2$,

-C(R_7)-N(R_6)$_2$,

-S(O)$_2$-N(R_6)$_2$,

-N(R_6)-C(R_7)-C_{1-10} alkyl,

-N(R_6)-S(O)$_2$-C_{1-10} alkyl,

-C(O)-C_{1-10} alkyl,

-C(O)-O-C_{1-10} alkyl,

-N_3,

-aryl,

-heteroaryl,

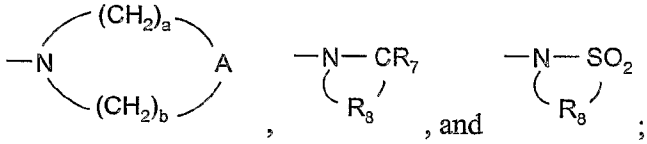
-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



, and ;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

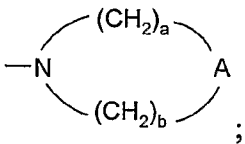
each R_7 is independently selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



;

Z is selected from the group consisting of -O- and -S(O)$_{0-2}$-; and

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_6)-, -N(Y-R_4)-, or -N(X-N(R_6)-Y-R_4)- then a and b are independently integers from 2 to 4;
or a pharmaceutically acceptable salt thereof.

20. The compound or salt according to claim 19 wherein R_1 is selected from the group consisting of -R_4, -Y-R_4, and -X-N(R_6)-Y-R_4 wherein Y is -C(R_7)-, -S(O)$_2$-, or -C(R_7)-N(R_9)-.

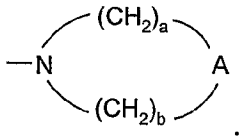
21. The compound or salt according to claim 20 wherein R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl, heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

22. The compound or salt according to claim 21 wherein R_1 is selected from the group consisting of hydrogen, methyl, isopropyl, butyl, 2-methylpropyl, 1-ethylpropyl, 3-methylbutyl, cyclohexyl, benzyl, cinnamyl, furan-2-ylmethyl, and –$CH_2CH_2CH_2$-NHR_{13}, wherein R_{13} is selected from the group consisting of methanesulfonyl, phenylsulfonyl, benzyl, and phenylaminocarbonyl.

23. The compound or salt according to claim 19 wherein R_1' is hydrogen.

24. The compound or salt of claim 19 wherein R_1 and R_1' are each independently alkyl.

25. The compound or salt of claim 19 wherein R_1 and R_1' join to form the group:



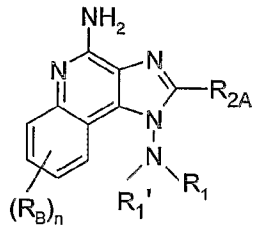
26. The compound or salt according to claim 19 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

27. The compound or salt according to claim 26 wherein R_2 is selected from the group consisting of hydrogen, butyl, 2-methoxyethyl, and ethoxymethyl.

28. The compound or salt according to claim 19 wherein n is 0.

29. The compound or salt according to claim 19 wherein n is 1, and R is halogen or hydroxy.

30. A compound of the Formula (I-3):



I-3

wherein:

R_B is selected from alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_1' is selected from hydrogen and alkyl;

R_1 is selected from:

$-R_4$,

$-Y-R_4$,

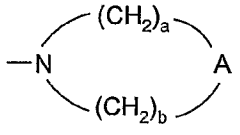
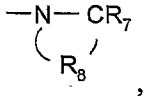
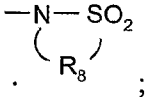
$-X-R_5$,

$-X-N(R_6)-Y-R_4$,

$-X-CR_7-N(R_6)-R_4$, and

$-X-O-R_4$;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from:



, and 
;

R_{2A} is selected from:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z- alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from:

-OH,

-halogen,

$-N(R_6)_2$,

$-CR_7-N(R_6)_2$,

$-SO_2-N(R_6)_2$,

$-N(R_6)-CR_7-C_{1-10}$ alkyl,

$-N(R_6)-SO_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

-heteroaryl,

-heterocyclyl,

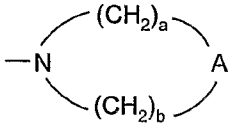
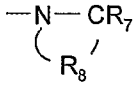
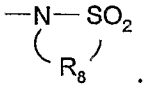
-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano,

carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from:

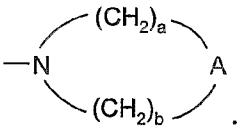

, 
, and 
;

R_6 is selected from hydrogen, alkyl, and arylalkylenyl;

R_7 is selected from =O and =S;

R_8 is C_{2-7} alkylene;

R_9 is selected from hydrogen, alkyl, and arylalkylenyl, or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group


;

A is selected from $-CHR_6-$, -O-, $-N(R_6)-$, $-N(Y-R_4)-$, and $-N(X-N(R_6)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from $-CR_7-$, $-SO_2-$, $-SO_2-N(R_6)-$, and $-CR_7-N(R_9)-$;

Z is selected from -O- and $-S(O)_{0-2}-$;

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

and pharmaceutically acceptable salts thereof.

31. The compound or salt according to claim 30 wherein R_1 is selected from $-R_4$, $-Y-R_4$, and $-X-N(R_6)-Y-R_4$ wherein Y is $-CR_7-$, $-SO_2-$, or $-CR_7-N(R_9)-$.

32. The compound or salt according to claim 31 wherein R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl,

heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

33. The compound or salt according to claim 32 wherein R_1 is selected from hydrogen, isopropyl, butyl, cyclohexyl, benzyl, cinnamyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from methanesulfonyl, phenylsulfonyl, benzyl, and phenylaminocarbonyl.

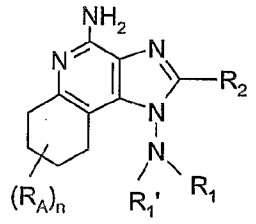
34. The compound or salt according to claim 30 wherein R_1' is hydrogen.

35. The compound or salt according to claim 30 wherein R_{2A} is selected from hydrogen, alkyl, and alkoxyalkylenyl.

36. The compound or salt according to claim 35 wherein R_{2A} is selected from hydrogen, butyl, methoxyethyl, and ethoxymethyl.

37. The compound or salt according to claim 30 wherein n is 0.

38. A compound of the Formula (II-1):



II-1

wherein:

each R_A is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio,
$-NH_2$,
-NH(alkyl), and
$-N(alkyl)_2$;

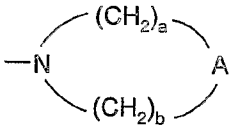
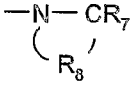
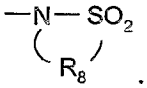
n is an integer from 0 to 4;

R_1' is selected from the group consisting of hydrogen and alkyl;

R_1 is selected from the group consisting of:

$-R_4$,
$-Y-R_4$,
$-X-R_5$,
$-X-N(R_6)-Y-R_4$,
$-X-C(R_7)-N(R_6)-R_4$, and
$-X-O-R_4$;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:


, 
, and 
;

R_2 is selected from the group consisting of:

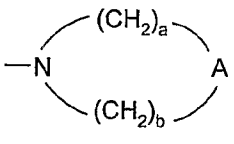
-hydrogen,
-alkyl,
-alkenyl,
-aryl,
-heteroaryl,
-heterocyclyl,
-alkylene-Z-alkyl,
-alkylene-Z-aryl,
-alkylene-Z-alkenyl, and

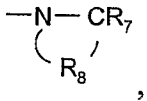
-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

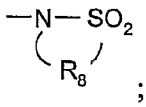
-OH,
-halogen,
-$N(R_6)_2$,
-$C(R_7)$-$N(R_6)_2$,
-$S(O)_2$-$N(R_6)_2$,
-$N(R_6)$-$C(R_7)$-C_{1-10} alkyl,
-$N(R_6)$-$S(O)_2$-C_{1-10} alkyl,
-$C(O)$-C_{1-10} alkyl,
-$C(O)$-O-C_{1-10} alkyl,
-N_3,
-aryl,
-heteroaryl,
-heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of:



,


, and


;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

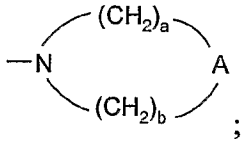
each R_7 is independently selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



;

Z is selected from the group consisting of -O- and -S(O)$_{0-2}$-; and

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_6)-, -N(Y-R_4)-, or -N(X-N(R_6)-Y-R_4)- then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

39. The compound or salt according to claim 38 wherein R_1 is selected from the group consisting of -R_4, -Y-R_4, and -X-N(R_6)-Y-R_4 wherein Y is -C(R_7)-, -S(O)$_2$-, or -C(R_7)-N(R_9)-.

40. The compound or salt according to claim 39 wherein R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl, heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

41. The compound or salt according to claim 39 wherein R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, arylalkylenyl, arylalkenylenyl, heteroarylalkylenyl, heteroarylalkenylenyl, aminoalkylenyl, alkoxyalkylenyl, acyl, alkylsulfonylaminoalkylenyl, arylsulfonylaminoalkylenyl, alkylaminocarbonyl, arylaminocarbonyl, (arylalkylenyl)aminoalkylenyl, heterocyclylcarbonylaminoalkylenyl, and arylaminocarbonylaminoalkylenyl.

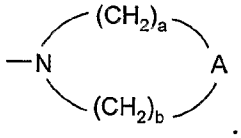
42. The compound or salt according to claim 40 wherein R_1 is selected from the group consisting of hydrogen, methyl, isopropyl, butyl, 2-methylpropyl, 1-ethylpropyl, 3-methylbutyl, cyclohexyl, benzyl, cinnamyl, furan-2-ylmethyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from the group consisting of methanesulfonyl, phenylsulfonyl, benzyl, and phenylaminocarbonyl.

43. The compound or salt according to claim 41 wherein R_1 is selected from the group consisting of hydrogen, methyl, isopropyl, butyl, 2-methylpropyl, 1-ethylpropyl, 3-methylbutyl, cyclohexyl, benzyl, 3-phenylpropyl, cinnamyl, furan-2-ylmethyl, and $-CH_2CH_2CH_2-NHR_{13}$, wherein R_{13} is selected from the group consisting of methanesulfonyl, phenylsulfonyl, benzyl, isopropylaminocarbonyl, morpholine-4-carbonyl, and phenylaminocarbonyl.

44. The compound or salt according to claim 38 wherein R_1' is hydrogen.

45. The compound or salt of claim 38 wherein R_1 and R_1' are each independently alkyl.

46. The compound or salt of claim 38 wherein R_1 and R_1' join to form the group:



47. The compound or salt according to claim 38 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

48. The compound or salt according to claim 47 wherein R_2 is selected from the group consisting of hydrogen, butyl, 2-methoxyethyl, and ethoxymethyl.

49. The compound or salt according to claim 47 wherein R_2 is selected from the group consisting of hydrogen, methyl, propyl, butyl, 2-methoxyethyl, and ethoxymethyl.

50. The compound or salt according to claim 38 wherein n is 0.

51. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 1 and a pharmaceutically acceptable carrier.

52. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 5 and a pharmaceutically acceptable carrier.

53. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 7 and a pharmaceutically acceptable carrier.

54. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 19 and a pharmaceutically acceptable carrier.

55. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 30 and a pharmaceutically acceptable carrier.

56. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 38 and a pharmaceutically acceptable carrier.

57. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 1 to the animal.

58. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 5 to the animal.

59. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 7 to the animal.

60. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 19 to the animal.

61. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 30 to the animal.

62. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 38 to the animal.

63. A method of treating a viral disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 1.

64. A method of treating a viral disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 5.

65. A method of treating a viral disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 7.

66. A method of treating a viral disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 19.

67. A method of treating a viral disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 30.

68. A method of treating a viral disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 38.

69. A method of treating a neoplastic disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 1.

70. A method of treating a neoplastic disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 5.

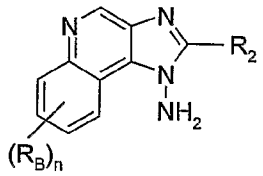
71. A method of treating a neoplastic disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 7.

72. A method of treating a neoplastic disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 19.

73. A method of treating a neoplastic disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 30.

74. A method of treating a neoplastic disease in an animal in need thereof comprising administering to the animal a therapeutically effective amount of a compound or salt of claim 38.

75. A compound of the Formula (VII):



VII

wherein:

each R_B is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,
-halogen,
-$N(R_6)_2$,
-$C(R_7)$-$N(R_6)_2$,
-$S(O)_2$-$N(R_6)_2$,
-$N(R_6)$-$C(R_7)$-C_{1-10} alkyl,
-$N(R_6)$- $S(O)_2$-C_{1-10} alkyl,
-C(O)-C_{1-10} alkyl,
-C(O)-O-C_{1-10} alkyl,
-N_3,
-aryl,
-heteroaryl,
-heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;

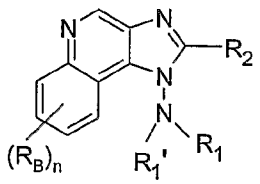
each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

R_7 is selected from the group consisting of =O and =S; and

Z is selected from the group consisting of -O- and -$S(O)_{0-2}$-;

or a pharmaceutically acceptable salt thereof.

76. A compound of the Formula (IX):



IX

wherein:

each R_B is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_1' is hydrogen or alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

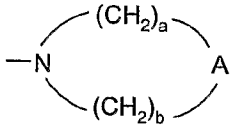
-X-R_5,

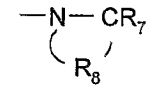
-X-N(R_6)-Y-R_4,

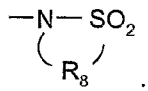
-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



,


, and


;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

-N(R_6)$_2$,

-C(R_7)-N(R_6)$_2$,

-S(O)$_2$-N(R_6)$_2$,

-N(R_6)-C(R_7)-C_{1-10} alkyl,

-N(R_6)- S(O)$_2$-C_{1-10} alkyl,

-C(O)-C_{1-10} alkyl,

-C(O)-O-C_{1-10} alkyl,

-N_3,

-aryl,

-heteroaryl,

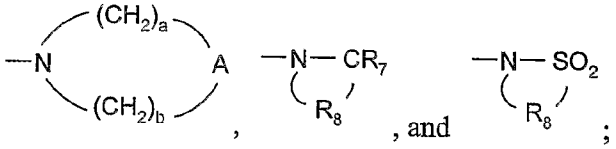
-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of



, , and ;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

each R_7 is independently selected from the group consisting of =O and =S;

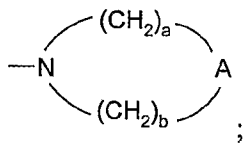
R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -$CH(R_6)$-, -O-, -$N(R_6)$-, -$N(Y\text{-}R_4)$-, and -$N(X\text{-}N(R_6)\text{-}Y\text{-}R_4)$-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -$C(R_7)$-, -$C(R_7)$-O-, -$S(O)_2$-,

$-S(O)_2-N(R_6)-$, and $-C(R_7)-N(R_9)-$; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



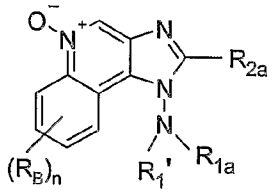
;

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$; and

a and b are independently integers from 1 to 4 with the proviso that when A is $-O-$, $-N(R_6)-$, $-N(Y-R_4)-$, or $-N(X-N(R_6)-Y-R_4)-$ then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

77. A compound of the Formula (X):



X

wherein:

each R_B is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

n is an integer from 0 to 4;

R_1' is hydrogen or alkyl;

R_{1a} is selected from the group consisting of:

$-R_{4a}$,

$-Y-R_{4a}$,

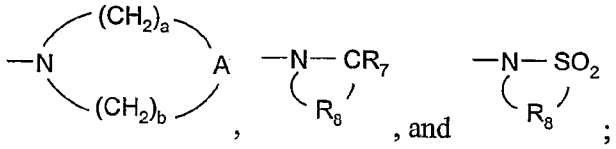
$-X-R_5$,

$-X-N(R_6)-Y-R_{4a}$,

$-X-C(R_7)-N(R_6)-R_{4a}$, and

$-X-O-R_{4a}$;

or R_1' and R_{1a} together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



, , and ;

R_{2a} is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-alkylene-Z"-alkyl,

-alkylene-Z"-aryl,

-alkylene-Z"- alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)-S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

-aryl,

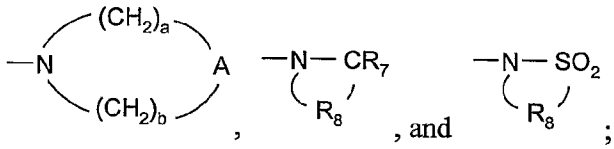
-heterocyclyl, and

-C(O)-aryl;

R_{4a} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl,

and heterocyclyl, oxo, with the proviso that when R_{4a} is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of



, and ;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

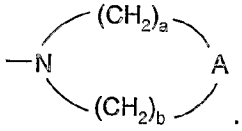
each R_7 is independently selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of -CH(R_6)-, -O-, -N(R_6)-, -N(Y-R_4)-, and -N(X-N(R_6)-Y-R_4)-;

X is C_{2-20} alkylene;

Y is selected from the group consisting of -C(R_7)-, -C(R_7)-O-, -S(O)$_2$-, -S(O)$_2$-N(R_6)-, and -C(R_7)-N(R_9)-; wherein R_9 is selected from the group consisting of hydrogen, alkyl and arylalkylenyl, or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group



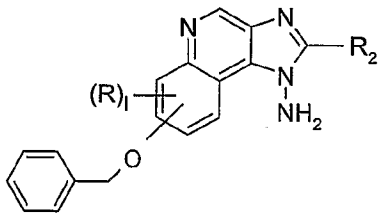
;

Z" is selected from the group consisting of -O- and -S(O)$_2$-; and

a and b are independently integers from 1 to 4 with the proviso that when A is -O-, -N(R_6)-, -N(Y-R_4)-, or -N(X-N(R_6)-Y-R_4)- then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

78. A compound of the Formula (XLII):



XLII

wherein:

R is selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

l is 0 or 1;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

$-N(R_6)_2$,

$-C(R_7)-N(R_6)_2$,

$-S(O)_2-N(R_6)_2$,

$-N(R_6)-C(R_7)-C_{1-10}$ alkyl,

$-N(R_6)-S(O)_2-C_{1-10}$ alkyl,

$-C(O)-C_{1-10}$ alkyl,

-C(O)-O-C_{1-10} alkyl,

-N_3,

-aryl,

-heteroaryl,

-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

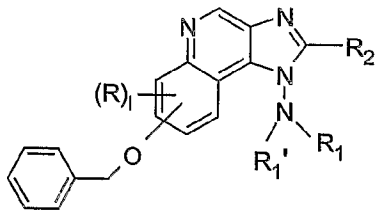
each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

R_7 is selected from the group consisting of =O and =S; and

Z is selected from the group consisting of -O- and -$S(O)_{0-2}$-;

or a pharmaceutically acceptable salt thereof.

79. A compound of the Formula (XLIII):



XLIII

wherein:

R is selected from the group consisting of alkyl, alkenyl, alkoxy, halogen, fluoroalkyl, hydroxy, amino, alkylamino, and dialkylamino;

l is 0 or 1;

R_1' is hydrogen or alkyl;

R_1 is selected from the group consisting of:

-R_4,

-Y-R_4,

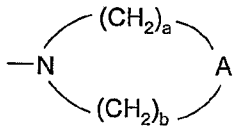
-X-R_5,

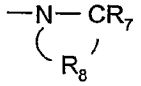
-X-N(R_6)-Y-R_4,

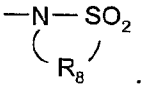
-X-C(R_7)-N(R_6)-R_4, and

-X-O-R_4;

or R_1' and R_1 together with the nitrogen atom to which they are bonded can join to form a group selected from the group consisting of:



, 

, and 

;

R_2 is selected from the group consisting of:

-hydrogen,

-alkyl,

-alkenyl,

-aryl,

-heteroaryl,

-heterocyclyl,

-alkylene-Z-alkyl,

-alkylene-Z-aryl,

-alkylene-Z-alkenyl, and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH,

-halogen,

-$N(R_6)_2$,

-$C(R_7)$-$N(R_6)_2$,

-$S(O)_2$-$N(R_6)_2$,

-$N(R_6)$-$C(R_7)$-C_{1-10} alkyl,

-$N(R_6)$- $S(O)_2$-C_{1-10} alkyl,

-C(O)-C_{1-10} alkyl,

-C(O)-O-C_{1-10} alkyl,

-N_3,

-aryl,

-heteroaryl,

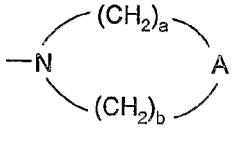
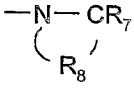
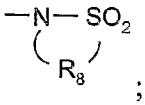
-heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, (arylalkylenyl)amino, dialkylamino, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, with the proviso that when R_4 is a substituted alkyl group and the substituent contains a hetero atom which bonds directly to the alkyl group then the alkyl group contains at least two carbons between the substituent and the nitrogen atom to which R_1 is bonded;

R_5 is selected from the group consisting of


, 
, and 
;

each R_6 is independently selected from the group consisting of hydrogen, alkyl, and arylalkylenyl;

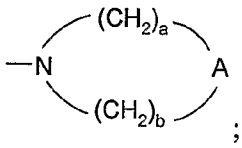
each R_7 is independently selected from the group consisting of =O and =S;

R_8 is C_{2-7} alkylene;

A is selected from the group consisting of $-CH(R_6)-$, -O-, $-N(R_6)-$, $-N(Y-R_4)-$, and $-N(X-N(R_6)-Y-R_4)-$;

X is C_{2-20} alkylene;

Y is selected from the group consisting of $-C(R_7)-$, $-C(R_7)-O-$, $-S(O)_2-$, $-S(O)_2-N(R_6)-$, and $-C(R_7)-N(R_9)-$; wherein R_9 is selected from the group consisting of hydrogen, alkyl, and arylalkylenyl; or R_9 and R_4 together with the nitrogen atom to which R_9 is bonded can join to form the group


;

Z is selected from the group consisting of -O- and $-S(O)_{0-2}-$; and

a and b are independently integers from 1 to 4 with the proviso that when A is

-O-, -N(R_6)-, -N(Y-R_4)-, or -N(X-N(R_6)-Y-R_4)- then a and b are independently integers from 2 to 4;

or a pharmaceutically acceptable salt thereof.

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